SYNTHESIS AND NMR STUDIES OF AROMATIC COMPOUNDS CONTAINING CROWDED METHOXY GROUPS

By

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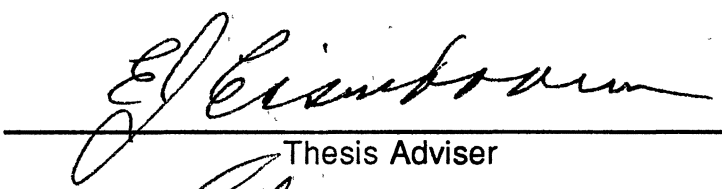

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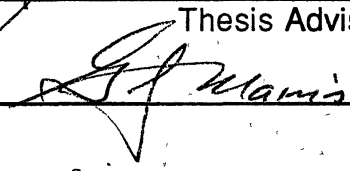

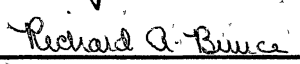

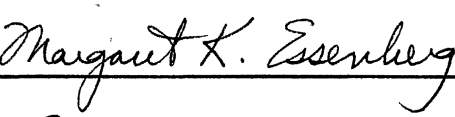

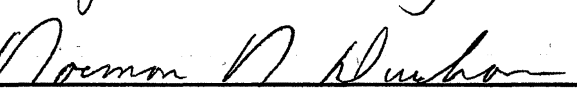

Dean of the Graduate College

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I wish to dedicate this thesis to all members of my wonderful family, who have given me the support and encouragement to obtain this degree: Shannon, whose love, understanding, and friendship has never ended and withstood my times of stress; my Dad, Papa, and Mommer who provided the necessary financial and emotional support throughout my under graduate and graduate studies; and Jay for being such a close friend and brother.

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LIST OF SYMBOLS AND ABBREVIATIONS

anhyd	anhydrous	Et	ethyl
Ar	aryl	g	gram
atm	atmosphere	GC	gas chromatography
bp	boiling point	h	hour(s)
br	broad (spectral)	HRMS	high-resolution mass spectrum
Bu	butyl	Hz	hertz
t-Bu	*tert*-butyl	IR	infrared
°C	degrees Celsius	*J*	coupling constant (NMR)
calcd	calculated	L	liter(s)
CAN	ceric ammonium nitrate	lit.	literature
cm	centimeter	μ	micro
CNDO	complete neglect of differential overlap	m	multiplet (spectral), milli
compd	compound	M	moles per liter
concd	concentrated	*m*-CPBA	*m*-chloroperbenzoic acid
δ	chemical shift in parts per million downfield from tetramethylsilane	*m/z*	mass to charge ratio (mass spectrometry)
d	doublet (spectral)	Me	methyl
DEPT	distorionless enhancement by polarization transfer	MHz	megahertz
EI	electron impact	min	minute(s)

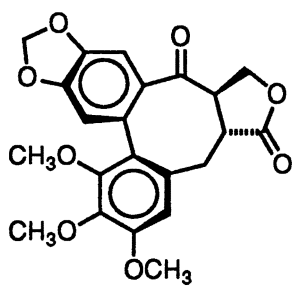
mL	milliliter
mol	mole(s)
mm	millimeter
mmol	millimole
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
ot	oven temperature (Kugelrohr distillation)
p	page; pentet (NMR)
PCC	pyridinium chlorochromate
pp	pages
PPA	poly(phosphoric acid)
ppm	parts per million (NMR)
i-Pr	isopropyl
PRDDO	partial retention of diatomic differential overlap
q	quartet (spectral)
s	singlet (NMR); second(s)
SCS	substituent chemical shift (NMR)
t	triplet (NMR)
TBAB	tetra-*n*-butylammonium bromide
TFA	trifluoroacetic acid
UV	ultraviolet

CHAPTER I

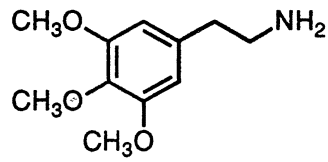
HISTORICAL BACKGROUND

Introduction

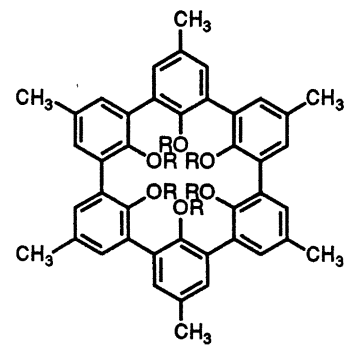
A myriad of publications concerning the methoxy group conformation in anisoles has appeared during the last 40 years.[1-6] This conformation has been suggested to play an important role in determining the hallucinogenic potency in polymethoxyphenethylamines.[7] Aromatic systems that contain methoxy groups are diverse and include: pharmacologically active substances,[7] naturally occurring plant and wood lignans,[8] enzyme inhibitors and substrates, liquid crystals,[9] spherands,[10] cavitands,[10] and calixarenes.[11] Equally important, in chemical and biochemical processes, are plant phenolics which upon methylation yield anisoles.[12-14] Representative structures are shown below.



(-)-Steganone
an antileukemic
lignan lactone



Mescaline
a physcoactive
drug

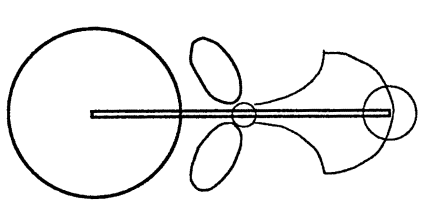


a spherand
R= Me

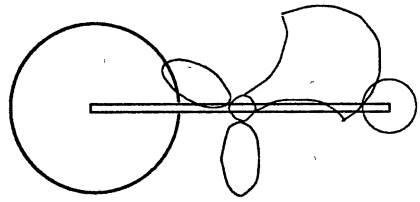
This chapter will emphasize spectroscopic properties of anisoles in relationship to the methoxy group conformation. To assist the reader a glossary of structures is provided on pp 74-81.

Conformations of Methoxy Groups

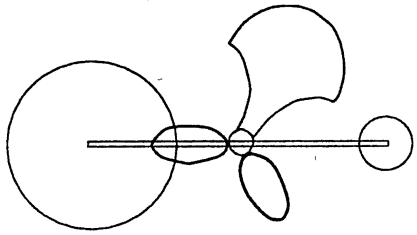
Anisole has been calculated to have an energy minimum with the methoxy group in a conformation nearly coplanar with the aromatic ring. The methoxy group is free to rotate about the C_{Ar}-O bond and the barrier to this rotation has been calculated to be 1.88 kcal/mol.[15] This value varies depending upon how the rotational barrier is determined (IR: 2.6 kcal/mol,[16] 6 kcal/mol;[17] Raman solid state: 11.53 kcal/mol[18]). The possible conformations resulting from such a rotation are shown in Figure 1 (p 3). In the model shown, the horizontal bar is the side view of the aromatic ring viewed along the O-C_{Ar} bond, the large circle to the left side of the molecule is an ortho substituent at the 2 position on the aromatic ring, while the smaller circle on the right is a hydrogen atom at the 6 position. The methoxy oxygen in this drawing is assumed to be sp^3 hybridized. X-ray analysis[19] of noncrowded anisoles, however, show bond angles and bond distances closer to those expected for sp^2 hybridization of the methoxy oxygen (vide infra). The methoxy group, in Figure 1,[20] has been rotated at 30° intervals to give eclipsed conformations **1a**, **1c**, **1e**, and **1g** while conformations **1b**, **1d**, and **1f** are staggered. Since eclipsed conformations are of a higher energy form than staggered ones, the preferred orientation of the methoxy group would be either **1b**, **1d**, or **1f**, and since the ortho substituent is blocking the methoxy methyl in **1f**, only **1b** and **1d** represent logical models. Between these, **1b** is the more resonable since one of the oxygen lone-pair orbitals is perpendicular to the aromatic ring and can



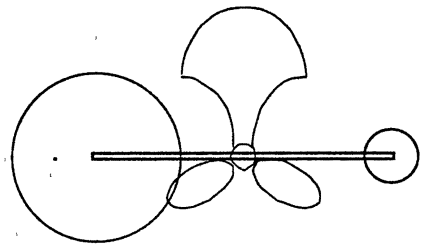
1a



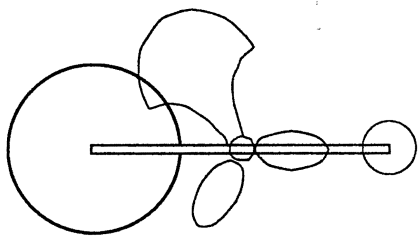
1b



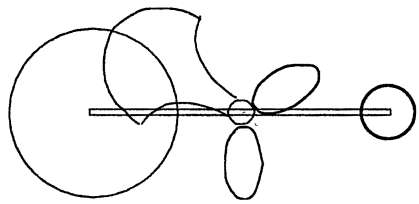
1c



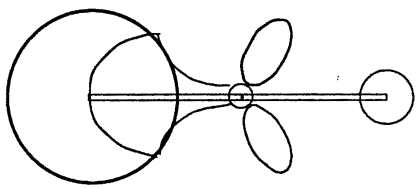
1d



1e



1f



1g

Figure 1. Possible conformations of a methoxy group relative to the aromatic ring in a 2-substituted anisole.[20]

overlap with the orbitals of the benzene π system. In crowded anisoles (simultaneous substitution at the 2 and 6 positions on the aromatic ring) conformation **1d** represents the minimum energy form. However, this conformation results in a loss of overlap between the methoxy oxygen lone-pair orbitals and the π system of the aromatic ring. From X-ray analysis of compounds containing crowded methoxy groups, bond angles at the methoxy oxygen are decreased and the O-Me bond is lengthened as compared to those of noncrowded methoxy groups. Thus, the methoxy oxygen approaches sp^3 hybridization (vide infra).

Resonance Effects of Methoxy Groups

The effect of methylation on the UV spectra of phenols in ethanol has been studied.[21] Methylation displaces both the B- and the K-bands to shorter wavelength and reduces the intensities of these signals. These results are expected since the methyl group, being more electron withdrawing than hydrogen, would decrease the electron release from the oxygen to the aromatic ring. If both of the ortho positions, relative to the methoxy group, are substituted, the observed wavelengths are displaced to shorter wavelengths by 70-100 Å and the intensity (molar extinction coefficient, ε_{max}) of the B-band is reduced by 70-80% as compared to those absorptions for the uncrowded anisoles, shown in Table I. This hypsochromic shift and the reduction in the intensity of the B-band observed for crowded anisoles, is typical for systems in which steric crowding decreases the interaction between the electron pair(s) of a heteroatom and the π-electrons of the aromatic ring.[22] Similar effects have been reported for the C-band of crowded anisoles dissolved in cyclohexane.[23]

TABLE I.[a] UV Absorptions for the B-Band of Phenols and Anisoles

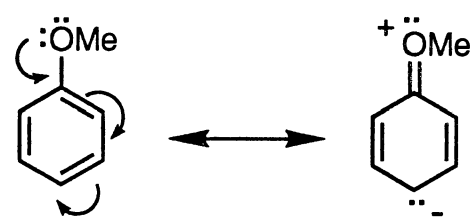
Substituent	Phenol		Anisole	
	λ (Å)	ε_{max}	λ (Å)	ε_{max}
none	2719	1875	2770	1400
p-Me	2802	2100	2845	1800
			2775	2100
2,6-diMe	2725	1800	2650	600
2,4,6-triMe	2785	1800	2772	500
			2686	575
p-Cl	2828	1850	2880	1600
			2813	1850
2,4,6-triCl	2941	2900	2874	875
			2805	875

[a] Taken from reference 21.

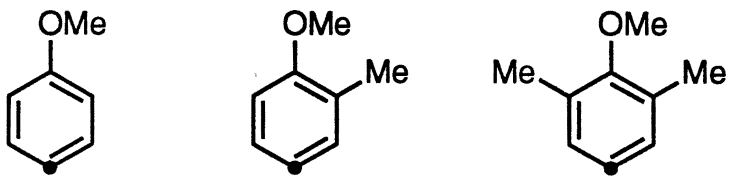
Dipole moments of anisoles have also been used to study the resonance interactions of a methoxy group with the aromatic ring. The data obtained from these studies, however, are not conclusive enough to fully describe the orientation of the methoxy group with respect to the aromatic ring.[24] They suggest that one ortho neighbor, next to a methoxy group, increases the dipole moment more than would be expected.[25] Introduction of a second ortho substituent, next to the methoxy group, decreases the dipole moment. This was explained by considering the conformations of the methoxy group. In Figure 1 (p 3), where both circles are hydrogen, the methoxy group can occupy two planar positions of equal energy, **1a** and **1g**. In order to convert between these two positions, rotation about the C_{Ar}-O bond takes place. This rotation takes the methoxy oxygen from being in conjugation (**1a**) with the aromatic ring (maximum overlap of oxygen *p*-orbitals with the π system of the aromatic ring)

to out of conjugation (**1d**) and then back in conjugation (**1g**). When an ortho substituent is present (large circle in Figure 1 is an alkyl group), the methoxy group occupies the planar conformation (**1a**) a larger percentage of the time. Conversion between the two planar conformations is reduced and the resonance interactions with the aromatic ring are enhanced. This 'steric enhancement of resonance' of the methoxy group increases the dipole moment for the 2-substituted anisole. When there are two ortho substituents present, the methoxy group is in conformation **1d** and the overlap between the methoxy oxygen and the aromatic system is decreased. This is 'steric inhibition of resonance' and it decreases the dipole moment for the *o,o'*-disubstituted anisoles.

The question of 'steric enhancement of resonance' and 'steric inhibition of resonance' for *o* - and *o,o'*-substituted anisoles, however, has been disputed. Dhami and Stothers[26] found little evidence for this from the ^{13}C NMR spectra of anisoles. Kitching[27] studied the effect by considering the para-carbon shift in the ^{13}C NMR spectra of anisole (**2a**), 2-methylanisole (**3**), and 2,6-dimethylanisole (**4a**), Figure 2 (p 7). The SCS (substituent chemical shift)[28] for the para-carbon gives some indication of the relative electron density at that carbon. Electron release from the methoxy group increases the electron density at the para-carbon and the ^{13}C NMR signal of the para-carbon is



shifted upfield. For anisole (**2a**), this signal is upfield by 7.68 ppm, relative to the signal for internal benzene.[28] 2-Methylanisole (**3**), where, the resonance was observed to be increased by the dipole moment studies, has a larger upfield shift (7.93 ppm, relative to internal toluene[28]). The crowded anisole (**4a**) has an upfield shift of only 4.45 ppm (relative to internal meta-xylene[28]). This supports the concept that the ortho substituent(s) effects the resonance interactions of the methoxy group with the aromatic ring (experimental error was reported at ±0.03 ppm).



SCS (ppm)	-7.68	-7.93	-4.45
	2a	**3**	**4a**

Figure 2. ^{13}C NMR SCS values for the para carbon in anisole, 2-methylanisole, and 2,6-dimethylanisole.[28]

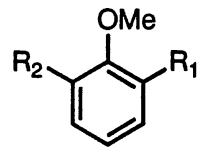
Schuster et al. has also studied the para-carbon chemical shifts of methoxy-substituted compounds.[29] The SCS corrected values for the ^{13}C NMR signals of the para carbon are listed in Table II (p 9). All para-carbon shifts are upfield from the ^{13}C resonance of benzene (128.31) by 4-8 ppm. As expected, the mono-ortho substituted compounds (**3**, **5**, **6**, **7a**, **8**) show more shielding than the di-ortho substituted (**4a**, **9**, **10a**, **11a**, **12a**, **13a**, **14**, **15**)

compounds. These data show that there is a significant amount of electron release from the crowded methoxy group to the para-carbon of the aromatic ring. For compound **10a** this amount of release was calculated to 55.6% of that for the planar molecule **6** by using the equation 1 shown below.[29]

$$\% \text{ resonance} = \frac{\delta\ ^{13}C(\text{benzene}) - \delta\ ^{13}C_4(\mathbf{10a})}{\delta\ ^{13}C(\text{benzene}) - \delta\ ^{13}C_4(\mathbf{6})} \times 100 \qquad (1)$$

For the di-ortho substituted compounds the shielding of the para-carbon signal decreases as the size of the ortho substituent increases until the ortho substituents become *t*-butyl groups. The para-carbon shift for 2,6-di-*t*-butylanisole (**11a**) is less than the shielding of the para-carbon of 2,6-dimethylanisole (**4a**) suggesting that there is more resonance interaction in **11a** than in **4a**. In order to compare the effect of different methoxy groups, the % resonance of compounds **4a**, **9**, **10a**, **11a**, **12a**, **13a**, **14**, and **15** relative to anisole (**2a**) has been calculated (see Table III, p 10). The compounds that have the most resonance interaction, based upon the values in Table III calculated from equation 1 (p 8), are the ones that have at least one ortho neighbor as a *t*-butyl group or an in-plane methoxy. The smallest is obtained for 2,6-di-*i*-propylanisole (**10a**).

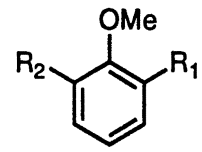
TABLE II.[a] SCS-Corrected[b] ^{13}C NMR Chemical Shifts of the Para Carbon in 2,6-Disubstituted Anisoles



compd	R_1	R_2	$\delta(^{13}C)$	$\Delta\delta(^{13}C)$[c]
2a	H	H	120.64	-7.67
3	Me	H	120.04	-8.27
5	Et	H	120.12	-8.19
6	*i*-Pr	H	120.30	-8.01
7a	*t*-Bu	H	120.29	-8.02
8	OMe	H	120.45	-7.86
4a	Me	Me	123.39	-4.92
9	Et	Et	123.53	-4.78
10a	*i*-Pr	*i*-Pr	123.86	-4.45
11a	*t*-Bu	*t*-Bu	122.91	-5.40
12a	*t*-Bu	Me	122.49	-5.82
13a	OMe	OMe	122.83	-5.48
14	OMe	Me	122.64	-5.67
15	OMe	*i*-Pr	123.05	-5.26

[a] Taken from reference 29. [b] See reference 28.
[c] Upfield from the resonance of benzene.

TABLE III. Percent Resonance of Substituted Anisoles Relative to Anisole



compd	R_1	R_2	% Resonance[a]
4a	Me	Me	64.1
9	Et	Et	62.3
10a	*i*-Pr	*i*-Pr	58.0
11a	*t*-Bu	*t*-Bu	70.4
12a	*t*-Bu	Me	75.9
13a	OMe	OMe	71.4
14	OMe	Me	73.9
15	OMe	*i*-Pr	68.6

[a] Calculated from equation 1, p 8, substituting the appropriate compound in place of **10a**, and anisole in place of **6**. Chemical shift values came from Table II (p 9).

The SCS corrected para-carbon NMR shift values show a good correlation with the previously reported IR frequencies.[29,30] This correlation, Figure 3, supports the resonance argument made for the para carbon shifts in the NMR of substituted anisoles and that electron delocalization is influenced by the size of the ortho substituent. The shielding values, listed in Table II (p 9), reflect the amount of electron release from the methoxy group and decrease in the following order: *t*-butyl > methoxy (in plane) > methyl > ethyl > *i*-propyl.

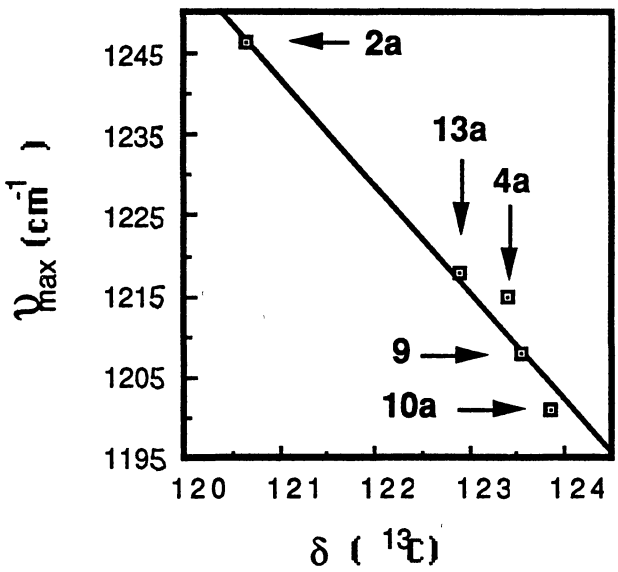


Figure 3. IR C_{Ar}-O stretching frequencies vs the SCS-corrected *p*-carbon ^{13}C NMR chemical shift for **2a**, **4a**, **9**, **10a**, and **13a**.[29]

NMR Studies of the Methoxy Group

Methoxy groups, attached to aromatic rings, that exist in a planar conformation with the ring have ^{13}C NMR chemical shift values very close to that of anisole (54.8 ppm). Nonplanar methoxy groups, have chemical shifts 5-9 ppm downfield from the signal of anisole.[26,31-34] Since the two kinds of methoxy groups, in-plane and out-of-plane, fall in different chemical shift ranges, ^{13}C NMR analysis provides a convenient test of conformation. PRDDO[33] and STO/3G[1] molecular orbital calculations have shown that the low-energy conformation for the crowded anisoles (two ortho substituents) has the methoxy carbon out of the plane of the aromatic ring. For the noncrowded case, the preferred orientation is coplanar with the aromatic ring. These calculations also show that the atomic charge on the crowded methoxy oxygen exceeds that of the methoxy oxygen of noncrowded anisoles and consequently

the charge on the crowded methoxy carbon is reduced (Figure 4).[33] This is expected since the orbitals of a crowded methoxy oxygen are rotated out of conjugation with the ring and thus electron delocalization is reduced. It is these changes in the charge densities on the methoxy methyl that have been used to explain the deshielding of a crowded methoxy ^{13}C NMR signal.[33]

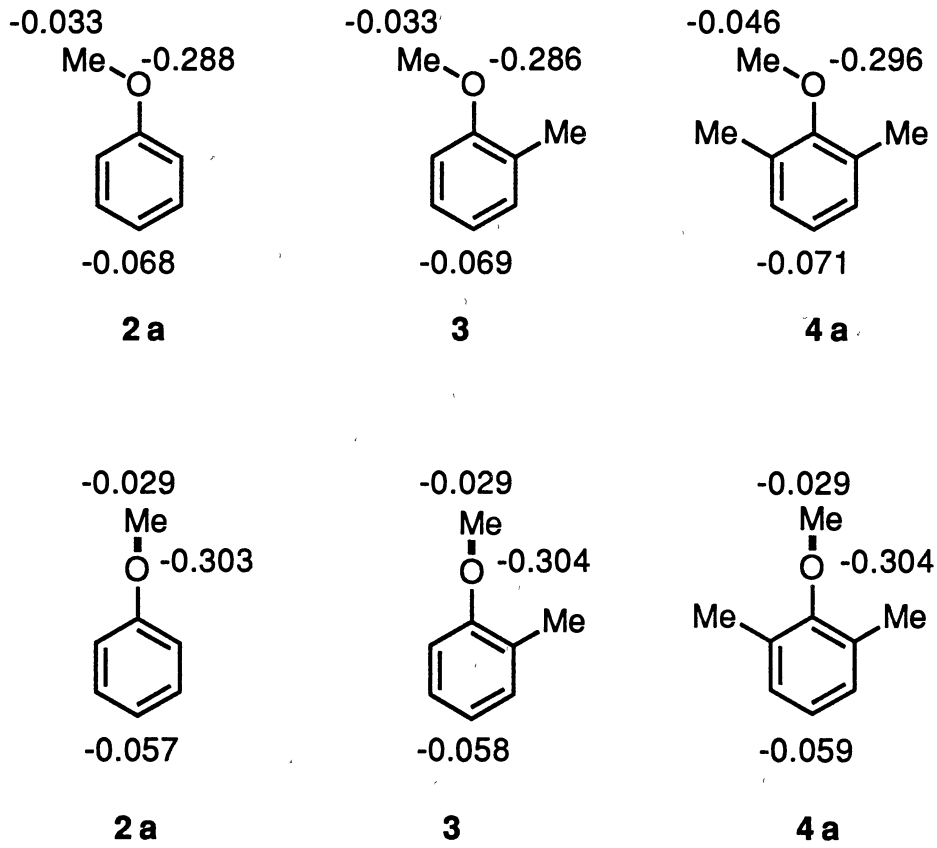
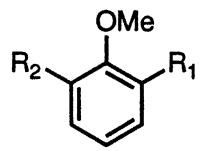


Figure 4. PRDDO MO calculated atomic charges for positions where the methoxy group is rotated 0° and 90° for **2a**, **3**, and **4a**.[33]

^{13}C NMR T_1 relaxation values for the methoxy carbon have also supported the nonplanarity of methoxy groups of crowded anisoles.[32,33] As shown below in Table IV, the T_1 values reported for the methoxy carbon are larger for the crowded anisoles (>7.0 s) than they are for the noncrowded ones (<6.5 s). Since the crowded methoxy groups are out of the plane of the aromatic ring, rotation about the O-Me bond is not hindered by the ortho substituents on the aromatic ring. Whereas, for a planar noncrowded methoxy group, this rotation is hindered by the aromatic hydrogen(s). Since the crowded anisoles (nonplanar methoxy) have faster rotation about the O-Me bond, the relaxation process is not as efficient and longer relaxation values result.

TABLE IV.[a] **^{13}C NMR T_1 Relaxation Values for the Methoxy Carbon of Anisoles**



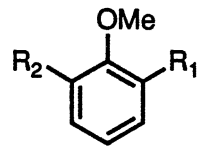
compd	R_1	R_2	T_1 Value (OMe), s
2a	H	H	6.5
3	Me	H	5.0
4a	Me	Me	11.4
9	Et	Et	9.2
10a	*i*-Pr	*i*-Pr	7.0
11a	*t*-Bu	*t*-Bu	8.2

[a] Taken from reference 33.

Oxygen-17 NMR of methoxy groups has proved useful in studying changes in the orientation of the methoxy group about the aromatic ring.[34,35] ^{17}O chemical shift changes are due primarily to alterations in the electron density at oxygen and correlate well with torsion angles for a variety of functional groups.[37] The signal for crowded anisoles appears upfield by 20-50 ppm relative to the signal for noncrowded anisoles, depending upon the size and electronic nature of the ortho substituents crowding the methoxy group.[35] This upfield shift is indicative of an increased electron density on the methoxy oxygen as a result of the reduction of electron delocalization to the aromatic ring. The magnitude of the ^{17}O NMR chemical shift increases as the size of the ortho substituent increases for 2,6-dialkyl substituted anisoles shown in Table V (p 15).[35] However, anomalous results are observed when one or more of the ortho substituents is a *t*-butyl group.

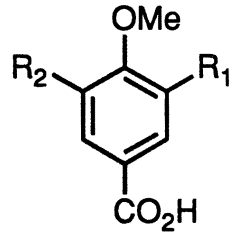
An explanation for the anomalous NMR results obtained for the *t*-butyl crowded anisoles have been derived from the X-ray analysis of 3,5-disubstituted anisic acids (**2b**, **4b**, **7b**, **10b**, **11b**, **12b**; structures shown on p 16) related to the 2,6-disubstituted anisoles.[29] The X-ray analysis showed a shortened C_{Ar}-O bond distance and a decreased C_{Ar}-O-Me bond angle for the crowded anisoles as presented in Table VI (p 16). These structural features show that the oxygen hybridization is closer to sp^3 in the crowded anisoles and to sp^2 hybridization in the noncrowded anisoles. Additionally the C_{Ar}-O bond distance of **2b**, **4b**, **7b**, **10b**, **11b**, and **12b** shows a good correlation with the para-carbon ^{13}C NMR chemical shift values of the parent anisoles **2a**, **4a**, **7a**, **10a**, **11a**, and **12a**.[29]

TABLE V.[a] ^{17}O NMR Chemical Shifts of the Methoxy Groups of Substituted Anisoles in $CDCl_3$[b]



compd	R_1	R_2	δ (ppm)
2a	H	H	48.0
3	Me	H	46.2
7a	*t*-Bu	H	48.8
8	OMe	H	33.5
4a	Me	Me	16.5
9	Et	Et	16.7
10a	*i*-Pr	*i*-Pr	13.5
11a	*t*-Bu	*t*-Bu	27.3

[a] Taken from reference 35. [b] Recorded at room temperature and reported downfield from the signal of external water.



	R_1	R_2
2b	H	H
4b	Me	Me
7b	*t*-Bu	H
10b	*i*-Pr	*i*-Pr
11b	*t*-Bu	*t*-Bu
12b	*t*-Bu	Me

TABLE VI.[a] Selected Structural Parameters for Anisic Acids and the Chromium Tricarbonyl Complex of 13a[b]

	C_1-OMe[c]	O-Me[c]	C_1-O-Me	P(Ar)P(C_1-O-Me)[d]
2b	1.356	1.435	118.1	3.2
7b	1.347	1.445	120.8	5.8
4b	1.381	1.417	115.5	90.8
10b	1.388	1.425	114.0	95.6
11b(A)[e]	1.396	1.420	115.9	95.4
11b(B)[e]	1.377	1.436	114.4	82.2
12b	1.374	1.424	116.5	58.6
13a·$Cr(CO)_3$	1.369	1.418	117.51	74.0

[a] Reference 29 . [b] Structure is shown on p 9 or in the glossary. [c] Bond distance (Å). [d] Angle methoxy group is rotated out of the plane of the aromatic ring. [e] Two molecules (A and B) of **11b** per unit cell.

Reactivity of Methoxy Groups

Regiospecific cleavage of crowded methoxy groups of anisoles to form the corresponding phenol has been observed. This demethylation is catalyzed by Lewis acids[39] (Figure 5), HBr/HOAc,[40] sodium thiophenolate,[41] and methanesulphonic acid in the presence of methionine.[42]

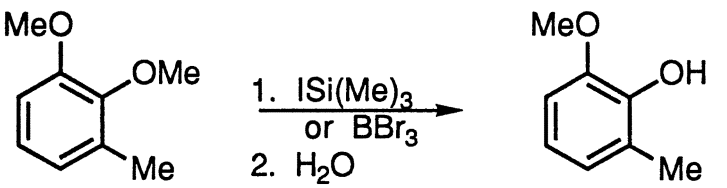


Figure 5. Regiospecific cleavage of a crowded aromatic methoxy group.[39]

The oxygen of a crowded methoxy group has a higher charge density than the oxygen of the noncrowded methoxy group.[33] This provides better complexation with the Lewis acid. Crowded methoxy groups also form a 1:1 complex with TFA.[43] This has been observed by examining the ^{13}C NMR spectra during the titration of 2,6-dialkylanisoles in $CDCl_3$ with TFA.

CHAPTER II

ELECTRONIC EFFECTS IN THE ^{13}C AND ^{17}O NMR SPECTRA OF CROWDED ANISOLES

Introduction

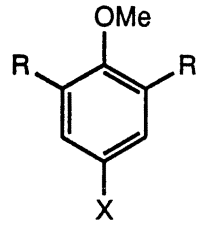
The methyl group of sterically crowded anisoles (two ortho neighbors or equivalent substitution) has previously been shown to undergo 5-9 ppm deshielding in the ^{13}C NMR spectrum as compared to uncrowded anisoles (one or no ortho neighbors).[26,31-33] As the size of the ortho substituents increase the magnitude of the downfield shift increases for 2,6-dialkylanisoles.[33] Crowding of the methoxy group forces rotation of the C_{Ar}-O bond so that the *O*-methyl group adopts a conformation out of the plane of the aromatic ring. This rotation decreases the overlap of the methoxy oxygen *p*-lone-pair orbitals with the π system of the aromatic ring, resulting in increased electron density on the crowded methoxy oxygen and correspondingly decreased electron density on the methoxy carbon. Thus, a downfield shift of the ^{13}C NMR signal for the methoxy group is observed. These electron density changes were suggested, on the basis of molecular orbital (STO-3G[1] and PRDDO[33]) calculations and supported by ^{17}O NMR studies.[35]

Evidence for decreased orbital overlap between the crowded methoxy oxygen and the aromatic ring also is supported by IR[30] and other NMR[44] spectroscopic data. Changes in the electron release from the crowded methoxy

groups to the aromatic ring, brought on by changing the size of the ortho substituents, has been detected at the para carbon.[27] The ^{13}C NMR signals for the ortho and para carbons of 2,6-crowded anisoles are shielded as compared to noncrowded anisoles, thus the electron density at these positions of the aromatic ring are decreased for the crowded system. Schuster[29] et al. showed, by examining the para-carbon shifts, that the electron release from a crowded methoxy group to the aromatic ring was greatly enhanced if at least one ortho substituent was a *t*-butyl group. However, this was only observed for the crowded anisoles. When the *t*-butyl substituent was next to a noncrowded methoxy group the NMR signal of the para carbon appeared at the normal position. Examination of the para carbon ^{13}C NMR signals for **4a**, **9**, **10a**, **11a**, and **13a** (Table II, p 9), showed that the electron release from the ether oxygen decreased following the order: *t*-butyl > methoxy (in-plane) >> methyl > ethyl > isopropyl. Additionally, the X-ray structures of 3,5-disubstituted-4-methoxybenzoic acids related to **4a**, **9**, **10a**, **11a**, and **13a**, show that the C_{Ar}-O bond length for the *t*-butyl substituted compound was shortened (**11b**, 1.377 Å; **4b**, 1.381 Å, **10b**, 1.388 Å), while the angle of rotation of the methoxy group from the plane of the aromatic ring was not changed appreciably (see Table VI, p 16). These observations suggest that steric bulk is less a controlling factor in determining the extent of the downfield ^{13}C NMR chemical shifts associated with the 2,6-di-*t*-butylanisoles **11**.[29]

^{17}O NMR studies, for a variety of functional groups, have shown that the oxygen NMR signal is highly sensitive to structural changes and dependent upon van der Waals interactions, torsional effects and electronic factors.[37] For noncrowded para-substituted anisoles (series **2**, p 20), the ^{17}O NMR signal of the methoxy oxygen varied from 36-67 ppm due to electronic effects from meta and para substituents,[36,38] and shows a good correlation with Hammett σ^-

values.[38] The correlation was improved by using the dual-substituent parameter approach, revealing that the chemical shift in series **2** was governed by resonance effects.[36] The ^{17}O chemical shifts were also correlated with the CNDO/2 π-bond order of the C_{Ar}-O bond as well as with the calculated π-electron density at methoxy oxygen.[38] Similar correlations have been shown to exist for Hammett σ values and the methoxy ^{1}H NMR chemical shifts[45] but not for methoxy carbon shifts.[26] Crowding of nonplanar methoxy groups, shields the methoxy oxygen signal by 20-50 ppm relative to the signal of anisole (48 ppm), depending upon the ortho substituents.[35] The magnitude of this upfield shift, has previously been shown to increase following the order OMe > *i*-Pr > Et > Me > *t*-Bu in a series of 2,6-disubstituted anisoles.



series	R
2	H
4	Me
9	Et
10	*i*-Pr
11	*t*-Bu
13	OMe

Results and Discussion

Since the electronic effect of a para substituent (X) on the NMR signal of a 2,6-crowded methoxy group was unknown, the NMR (^{1}H, ^{13}C, and ^{17}O) spectra of several series of such anisoles were obtained. The crowded

anisoles chosen for this study were the 4-substituted 2,6-dimethylanisoles (series **4**), 4-substituted 2,6-di-*t*-butyl anisoles (series **11**), and 1-substituted 3,4,5-trimethoxybenzenes (series **13**). Series **4** and **11** were included to further investigate the large difference in the ^{13}C and ^{17}O NMR spectral properties of their methoxy groups and to examine the steric differences that exist.

The synthesis of compounds in series **4** is shown in Figure 6 (p 22). 2,6-dimethylanisole (**4a**) was acetylated, nitrated, brominated, and formylated to give **4c**, **4g**, **4h**, and **4i**. The acetophenone (**4c**) was reacted with *m*-CPBA to give acetate **4d** which was hydrolyzed to give **4e** and then methylated to afford **4f**. The benzaldehyde (**4i**), formed by the reaction of **4a** with hexamethylenetetraamine in refluxing trifluoroacetic acid,[46] was converted to nitrile **4j**, by dehydration of the intermediate aldoxime in refluxing acetic anhydride.

Methylation of commercially available 4-substituted 2,6-di-*t*-butylphenols produced **11h**, **11i**, **11j**, and **11k**, (X = OMe, Me, Et, *t*-Bu). The syntheses of **11c-11g** (X = CO_2Me, CH_2OH, CHO, CN, and Br) are shown in Figure 7 (p 23).

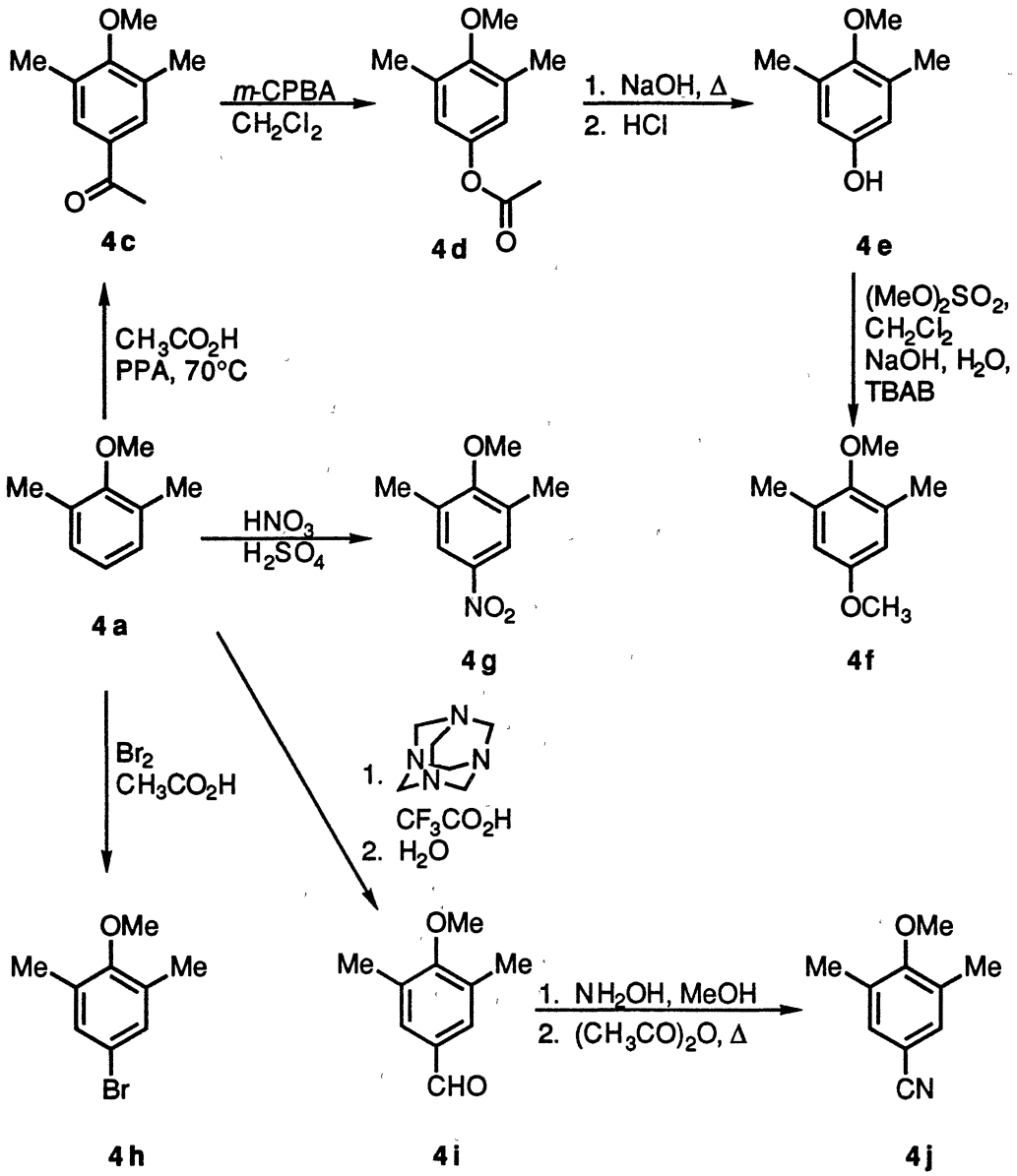


Figure 6. Reaction scheme for the synthesis of compounds in series **4**.

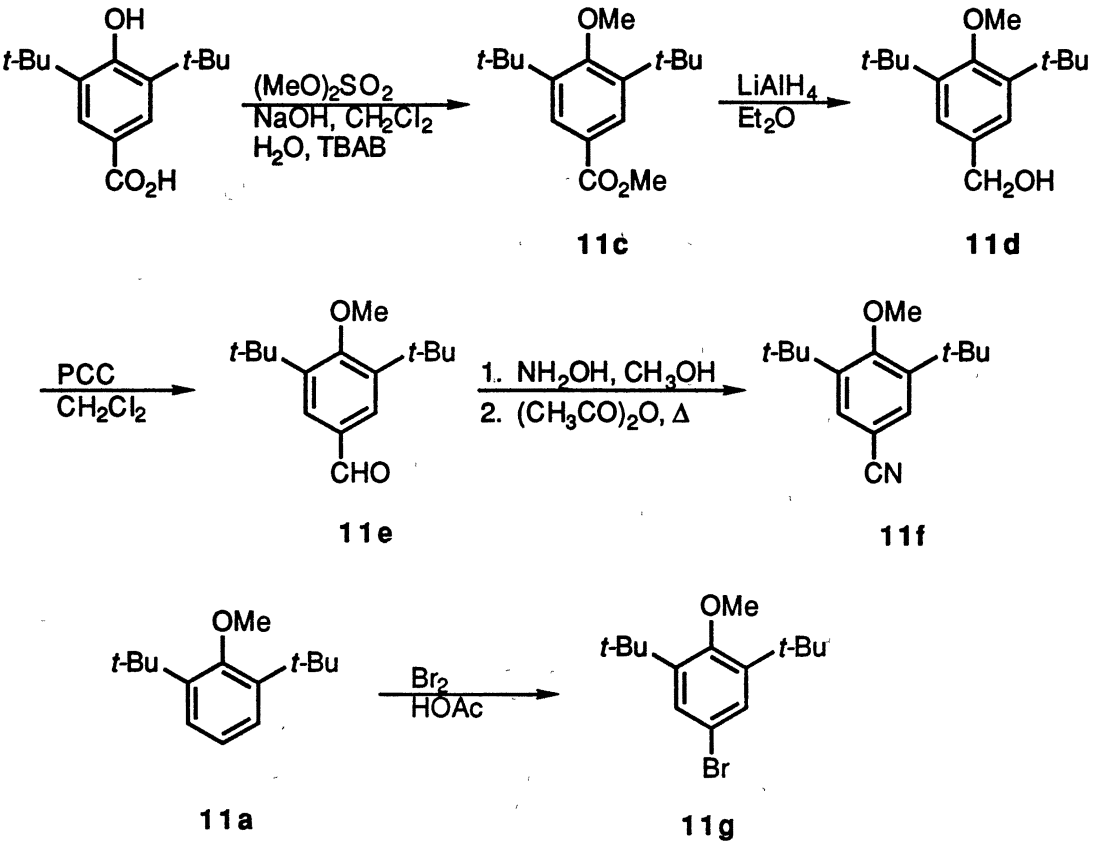
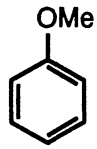
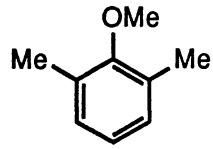


Figure 7. Reaction scheme for the synthesis of compounds in series **11**.

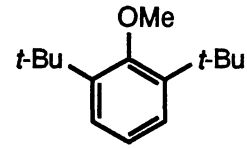
The ^{17}O NMR chemical shifts of the methoxy oxygen for series **2**, **4**, **11**, and **13** are listed in Table VII (p 25). The structures **2a**, **4a**, **11a**, and **13a**, shown on p 25, are the parent compounds for these series and a given structure in Table VII can be derived by substitution of the appropriate group at the para position of the methoxy group in **2a**, **4a**, **11a**, and **13a** (central methoxy group in this case). As reported earlier for series **2**,[38] electron withdrawing substituents deshield the methoxy oxygen NMR signal. A dual-parameter treatment[47] of the sigma (σ_p^+, σ_p^-) values gives good correlations with the observed ^{17}O NMR chemical shift values (Figure 8, p 26). The largest slope of the correlation lines, obtained for the noncrowded anisoles **2**, is 12.28. This shows, as expected, that the noncrowded methoxy group (planar) has the greatest resonance interactions with the para substituent. For the other three series of compounds, **4**, **11**, and **13**, slopes of 6.82, 7.14, 8.31 were obtained. The ratio of the slope of the correlation line for a crowded methoxy group to that of the noncrowded one (**4**, 55.5%; **11**, 58.1%; **13**, 67.7%) compares in magnitude to the values of the percent resonance for a crowded methoxy group relative to a noncrowded one (see Table III, p 10).[29] The least amount of interaction of the methoxy group with the aromatic ring is obtained for the 2,6-dimethylanisoles, series **4**, rather than the 2,6-di-*t*-butylanisoles, series **11**, which contain the larger *t*-butyl groups. This observation has been noted previously[29] but the order for the methoxy ortho substituted compound in series **13**, was different.



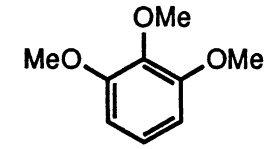
2a



4a



11a

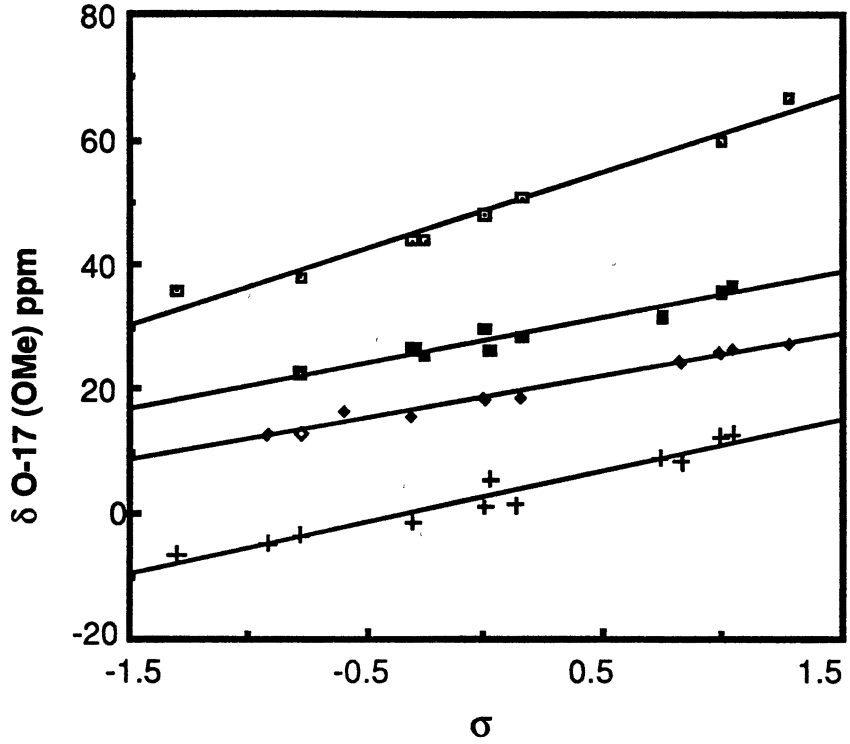


13a

TABLE VII. ^{17}O NMR Chemical Shift Values for Para-Substituted Anisoles

substituent	2[a]	4[b]	11[b]	13[b]
NH_2	36			-6.3
OH		13.1		-4.3
OMe	38	13.3	22.9	-3.0
t-Bu	44		25.7	
Me	44	16.1	26.6	-1.0
Et			26.9	
SMe		16.9		
O_2CMe		17.6		
Br	51	19.0	28.9	
H	48	19.1	29.7	1.6
CH_2CN				1.7
CH_2OH			26.3	1.5
COMe		24.7		8.7
CO_2H				9.3
CO_2Me			31.8	
CN	60	26.4	35.8	12.9
CHO		26.6	36.9	13.2
NO_2	67	27.8		

[a] Taken from reference 38. [b] Recorded at 75 °C in CH_3CN and referenced to external water.



▫	**2**	δ = 12.28σ + 48.87 ppm	r = 0.985	n = 8	(2)
◆	**4**	δ = 6.82σ + 19.17 ppm	r = 0.989	n = 10	(3)
▪	**11**	δ = 7.14σ + 28.24 ppm	r = 0.965	n = 10	(4)
+	**13**	δ = 8.31σ + 3.21 ppm	r = 0.973	n = 11	(5)

Figure 8. Plot and equations of ^{17}O NMR chemical shifts for the methoxy oxygen of series **2**, **4**, **11**, and **13** against Hammett substituent constants σ_p^+, σ_p^-.

The ^{17}O NMR spectra of 2,6-diethylanisole (**9**) and 2,6-diisopropylanisole (**10**) were obtained at 75 °C in acetonitrile and the data are shown in Table VIII along with that of other 2,6-disubstituted anisoles. As expected, these chemical shifts are slightly different from those obtained in chloroform at room temperature (see Table V, p 15). However, these data fit in the order of electron release as determined by the para substituent in the ^{13}C NMR.[29]

TABLE VIII. ^{17}O NMR Chemical Shift Values for 2,6-Disubstituted Anisoles in CH_3CN[a]

compd	R_1	R_2	δ ^{17}O NMR (ppm)
2a	H	H	48.8
4a	Me	Me	19.1
9	Et	Et	16.1
10a	*i*-Pr	*i*-Pr	14.4
11a	*t*-Bu	*t*-Bu	29.7
13a	OMe	OMe	1.6

[a] Recorded at 75 °C and referenced to external water.

The ^{13}C NMR signals of the 2,6-crowded methoxy groups are listed in Tables IX, X, XI (pp 29-31). These data show that the electronic effects induced by a para substituent are not an important factor in producing the large 5-9 ppm downfield shift of the 2,6-crowded methoxy groups. The signals for the crowded methoxy carbon cover a very small range in all three series of compounds studied: **4**, 0.44 ppm; **11**, 0.75 ppm; **13**, 0.44 ppm. The Hammett σ parameters did not show a good correlation with these chemical shift values. These data

lead to the conclusion that the conformational change of the methoxy group from in-plane to out-of-plane has a far greater effect on the position of the ^{13}C NMR signals of the methoxy group. We feel that the examples presented here support the claim that *^{13}C NMR deshielding of crowded methoxy groups can be used as a reliable predictive tool to support or deny structure assignment.*

As can be seen from the ^{13}C NMR data given in Tables IX, X, and XI (pp 29-31), the signals most affected by the para substituent are C_1, C_3 (ortho to X), and C_4 (ipso for X). C_1 should also give some indication of the resonance interaction of the para substituent (X) with the crowded methoxy group. The ^{13}C NMR signals for C_1 (crowded methoxy group attachment) give good correlations with the Hammett substituents constants. The equations of the correlation lines are shown in Figure 9. Para electron withdrawing substituents cause increased deshielding of the ^{13}C NMR signal for C_1. This is expected since the resonance interaction of the methoxy oxygen with an electron withdrawing para substituent would increase the double bond character between the methoxy oxygen and C_1 and hence the deshielding.

4	$\delta = 5.47\sigma + 156.31$ ppm	$r = 0.971$	$n = 10$	(6)
11	$\delta = 6.14\sigma + 158.55$ ppm	$r = 0.985$	$n = 10$	(7)
13	$\delta = 5.88\sigma + 137.31$ ppm	$r = 0.972$	$n = 11$	(8)

Figure 9. Equations of the plots of ^{13}C NMR chemical shifts for C_1 of series **4**, **11**, and **13** against Hammett substituent constants σ_p^+, σ_p^-.

TABLE IX. ^{13}C NMR Chemical Shift Values for Compounds in Series 4

compd		Me	OMe	C_1	C_2	C_3	C_4	X
4a	H	16.03	59.53	156.98	130.80	123.75	123.79	
4b	CO_2H	16.16	59.68	161.82	131.23	131.16	124.51	172.14
4c	COMe	16.25	59.67	161.26	131.15	129.42	132.88	197.64
								26.54
4d	O_2CMe	16.14	59.63	154.55	131.95	121.38	146.11	169.77
								20.98
4e	OH	16.13	59.95	151.17	131.94	114.98	150.74	
4f	OMe	16.31	59.93	155.28	131.64	113.62	150.78	55.39
4g	NO_2	16.37	59.87	162.39	132.31	124.24	143.47	
4h	Br	15.91	59.72	156.11	133.08	131.39	116.29	
4i	CHO	16.17	59.66	162.40	131.91	130.69	132.26	191.59
4j	CN	16.01	59.80	160.84	132.54	132.78	119.05	107.38
4k	Me	15.97	59.73	154.73	130.45	129.37	133.07	20.66
4l	SMe	16.07	59.97	155.10	131.54	127.76	132.38	16.81

TABLE X. ^{13}C NMR Chemical Shift Values for Compounds in Series 11

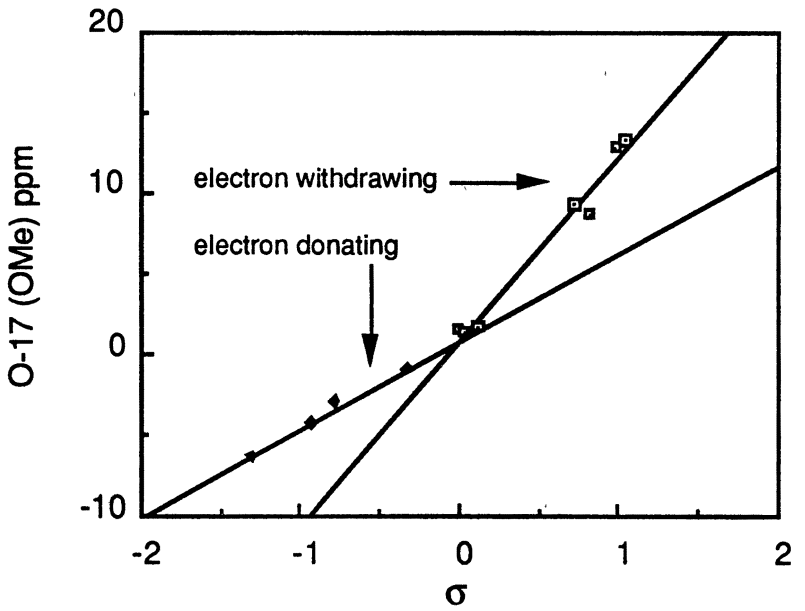
compd		Me	C	OMe	C_1	C_2	C_3	C_4	X
11a	H	32.1	35.7	64.2	159.5	143.6	126.5	122.9	
11c	CO_2Me	31.92	35.87	64.40	163.85	144.01	128.25	124.39	167.44
									51.92
11d	CH_2OH	32.07	35.75	64.21	159.05	143.78	125.57	134.81	65.62
11e	CHO	31.85	35.94	64.55	165.36	145.06	128.62	131.36	192.12
11f	CN	31.72	35.99	64.67	163.61	145.54	130.78	119.76	106.80
11g	Br	31.87	35.93	64.37	158.70	146.00	129.51	116.37	
11h	OMe	32.04	35.96	64.22	154.32	144.46	111.76	153.33	55.21
11i	Me	32.10	35.60	64.16	157.28	143.22	127.19	131.56	21.31
11j	Et	32.16	35.68	64.09	157.34	143.12	125.88	137.82	28.7
									15.63
11k	*t*-Bu	32.20	35.88	63.92	156.88	142.30	123.42	144.40	34.56
									31.58

TABLE XI. ^{13}C NMR Chemical Shift Values for Compounds in Series 13[a]

compd		OMe	$(OMe)_2$	C_1	C_2	C_3	C_4	X
13a	H	60.81	56.06	138.14	153.54	105.23	123.65	
13b	OH	61.10	55.90	131.34	153.66	92.97	152.79	
13c	OMe	61.04	56.09	132.25	153.74	91.68	156.26	61.03
13d	Me	60.86	56.00	133.59	153.02	105.95	135.79	21.85
13e	NH_2	61.06	55.90	130.71	153.87	92.64	142.97	
13f	CH_2OH	60.66	55.84	137.49	153.10	103.63	136.74	64.44
13g	CH_2CN	60.88	56.22	137.74	153.71	105.06	125.39	123.83
13h	CO_2H	60.95	56.24	142.98	152.95	107.42	124.14	171.94
13i	CN	61.06	56.40	142.35	153.58	109.46	118.98	106.73
13j	CHO	60.99	56.28	143.60	153.65	106.99	131.73	191.05
13k	COMe	60.89	56.30	142.80	153.12	105.95	132.52	196.72
								26.12

[a] Compounds in this table are numbered as 4-substituted-2,6-dimethoxyanisoles.

Plotting the ^{17}O chemical shifts (Table VII, p 25) for series **4**, **11**, and **13** (series are defined on p 20) against electron withdrawing (σ_p^+) and electron donating (σ_p^-) substituent constants separately, two correlation lines are obtained for each series. For series **4** and **11** the slopes of these two lines are approximately equal. Series **13** has two correlation lines with drastically different slopes as shown in Figure 10.

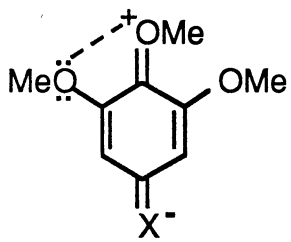


◆ $\delta = 5.41\sigma_p^- + 0.83$ ppm r = 0.993 n = 4 (9)

⊡ $\delta = 11.40\sigma_p^+ + 0.87$ ppm r = 0.985 n = 7 (10)

Figure 10. Plot and equations of ^{17}O NMR chemical shifts for the methoxy oxygen of series **13** against Hammett substituent constants σ_p^+, σ_p^-.

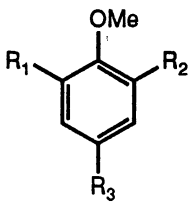
For the latter group, series **13**, the resonance effects are enhanced (compare the slopes of the regression lines: 5.41 in eq 9, and 11.40 in eq 10) with the electron withdrawing substituents. For structures of this type, a positive charge is forming on the methoxy oxygen of the crowded methoxy group. The ortho substituents are methoxy groups (coplanar with the ring) in a conformation such that the methyl lies in the plane of the ring away from the crowded methoxy (out of plane). The unshared electron pairs on the coplanar methoxy groups are thus directed toward the crowded methoxy group and can interact with the developing positive charge on the crowded methoxy group. This interaction increases the double bond character of the C_{Ar}- O bond and thus produces the increased deshielding effect.



The ^{17}O NMR spectra of compounds **16-24** (Table XII) were also recorded. The data from these compounds and that of pentafluoroanisole **25** (δ 7.0 ppm), show that the upfield chemical shift of the ^{17}O NMR signal for a crowded methoxy group is common for other functional groups, in the ortho position(s), crowding the methoxy group. An attempt was made to obtain the

^{17}O NMR spectrum of 2,4,6-triiodoanisole but the sample solubility in acetonitrile was inadequate at 75 °C.

Table XII. ^{17}O NMR Chemical Shifts[a] of Various Anisoles



compd	R_1	R_2	R_3	δ ^{17}O NMR (ppm)
16	Me	CHO	H	17.8
17	OMe	OH	H	1.1
18	Br	H	H	55.4
19	Br	Br	Br	36.3
20	Cl	H	H	49.8
21	Cl	Cl	H	27.8
22	Cl	Cl	Cl	29.2
23	*t*-Bu	Br	*t*-Bu	29.3
24	Ph	Ph	H	16.5

[a] Recorded at 75 °C in CH_3CN and referenced to external water.

Experimental Section for Chapter II

General Experimental Details: ^{1}H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, on a Varian XL-300 NMR spectrometer. Chemical shifts are reported in ppm or δ values downfield from TMS in $CDCl_3$ solvent. ^{17}O NMR spectra were recorded as 0.5 M solutions at 75 °C in acetonitrile on a Varian XL-400 NMR spectrometer equipped with a 10 mm broad band probe. ^{17}O NMR chemical shifts are referenced to external water. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Mass spectra data were obtained at 70 eV on a VG TS-250 or a VG ZAB-2SE (HRMS) instrument operating in the electron impact (EI) mode. Gas Chromatography analysis were performed on a Micro Tek 220 instrument using a U-shaped (6 ft x 0.25 in) glass column. All distillations were carried out in a Kugelrohr apparatus and boiling points refer to the oven temperature (ot) at time of distillation. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

3,5-Dimethyl-4-methoxyacetophenone (4c). 2,6-Dimethylanisole (126 g, 0.93 mol), PPA (1324 g), and acetic anhydride (65.5 g, 0.64 mol) were stirred for 2 h at 50 °C. The reaction was cooled, ice water was added, the mixture was shaken with toluene (3 x 700 mL), and the combined extracts were washed ($NaHCO_3$, NaCl), dried ($MgSO_4$) and filtered. Removal of toluene (rotary evaporator) and Kugelrohr distillation gave **4c** (141.4 g, 86%); mp 38-40 °C (EtOH / H_2O); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H), 2.55 (s, 3 H), 3.76 (s, 3 H), 7.64 (s, 2 H); ^{17}O NMR (CH_3CN) δ 24.7 (OMe at C_4), 544.2 (C=O); IR (CCl_4) 2830, 1670 cm^{-1}; MS *m/z* 178 (50.6), 163 (100).

3,5-Dimethyl-4-methoxyphenyl Acetate (4d).[48] A magnetically stirred solution of **4c** (34 g, 0.2 mol), *m*-CPBA (50.6 g, 0.24 mol) and CH_2Cl_2

(800 mL) was heated at reflux for 25 h. The reaction was cooled, filtered, and the filtrate concd (rotatory evaporator). The residue was dissolved in ether (600 mL), washed ($NaHCO_3$, 2% NaOH, H_2O), dried ($MgSO_4$) and filtered. Removal of the ether (rotary evaporator) and Kugelrohr distillation (85-110 °C ot, 0.35 mm) gave **4d** (35.1 g, 90.5%); mp 43-45 °C; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.27 (s, 6 H), 3.66 (s, 3 H), 6.71 (s, 2 H); MS *m/z* 194 (22.0), 152 (79.4), 137 (100).

3,5-Dimethyl-4-methoxyphenol (4e). The acetate **4d** (13.25 g, 68 mmol) and 150 mL of 20% NaOH were heated, under a nitrogen atm, at reflux for 2 h. The resulting yellow solution was cooled to room temperature and extracted with ether to give 2.07 g of **4d**. The aqueous layer was acidified and extracted with ether (3 x 100 mL). The combined ether extracts were washed (H_2O, NaCl), dried ($MgSO_4$), filtered, and concd (rotary evaporator) to give **4e** (8.68 g, 99% corrected for recovered starting material); mp 83-85 °C (pet ether / toluene); ^1H NMR ($CDCl_3$) δ 2.22 (s, 6 H), 3.78 (s, 3 H), 4.57 (s, 1 H), 6.49 (s, 2 H); ^{17}O NMR (CH_3CN) δ 13.1 (OMe at C_4), 70.9 (OH).

2,6-Dimethyl-4-methoxyanisole (4f). The phenol **4e** (8.68 g, 57 mmol) was methylated according to the procedure given for **11h** to give **4f** (8.92 g, 94%); ^1H NMR ($CDCl_3$) δ 2.27 (s, 6 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 6.55 (s, 2 H); ^{17}O NMR (CH_3CN) δ 13.3 (OMe at C_1), 42.4 (OMe at C_4).

2,6-Dimethyl-4-nitroanisole (4g).[49] 2,6-Dimethylanisole (**4a**) (0.68 g, 5 mmol) was added dropwise (15 min) to a flask containing HNO_3 (70%, 4.2 mL), cooled to 8 °C with an ice bath. The reaction was stirred magnetically for 30 min, poured into 50 mL of ice water, and shaken with ether (3 x 40 mL). The ether layers were combined, washed ($NaHCO_3$, NaCl), dried ($MgSO_4$), filtered and concd (rotary evaporator) to give a brown solid (0.73 g) which was passed through alumina (15 g acidic / 15 g basic) with low boiling petroleum ether to

yield **4g** as an off-white solid (0.609 g, 67%); mp 86-89 °C (lit[50] 92 °C); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6 H), 3.79 (s, 3 H), 7.92 (s, 2 H); ^{17}O NMR (CH_3CN) δ 27.8 (OMe), 571.6 (NO_2); MS *m/z* 181 (100), 166 (8.5).

4-Bromo-2,6-dimethylanisole (4h).[49] 2,6-Dimethylanisole (**4a**) (6.80 g, 50 mmol) was brominated according to the procedure give for **11g** to give **4h** (10.3 g, 96%); bp 90-110 °C ot, 0.50 mm; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 6 H), 3.69 (s, 3 H), 7.14 (s, 2 H); ^{17}O NMR (CH_3CN) δ 19.0; IR (neat) 2830, 1375 cm^{-1}; MS *m/z* 216 (96.4), 214 (100), 201 (65.3), 199 (67.9).

3,5-Dimethyl-4-methoxybenzaldehyde (4i).[46] 2,6-Dimethylanisole (**4a**) (6.80 g, 50 mmol), hexamethylenetetramine (14.0 g, 100 mmol) and trifluoroacetic acid (150 mL) were heated at reflux for 12 h. The cooled mixture was concd (rotary evaporator), combined with 600 mL of ice water, stirred for 15 min, made basic (Na_2CO_3) and extracted with ether (3 x 100 mL). The combined ether extracts were washed (NaCl), dried ($MgSO_4$), filtered and concd (rotary evaporator) to give **4i** (5.33 g, 65%); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H), 3.77 (s, 3 H), 7.54 (s, 2 H), 9.86 (s, 1 H); ^{17}O NMR (CH_3CN) δ 26.6 (OMe), 554.0 (C=O); MS *m/z* 164 (100), 146 (92.5).

3,5-Dimethyl-4-methoxybenzonitrile (4j). The aldehyde **4i** (4.10 g, 25 mmol) was used to prepare **4j** according to the procedure given for **11f**; Yield 3.43 g, 85%; mp 48-49 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6 H), 3.76 (s, 3 H), 7.32 (s, 1 H); ^{17}O NMR (CH_3CN) δ 26.4; MS *m/z* 161 (100), 146 (92.5).

2,4,6-Trimethylanisole (4k).[50] Methylation of 2,4,6-trimethylphenol (6.80 g, 50 mmol) according to the general procedure given for **11h** gave **4k**; Yield 6.84 g, 91%; bp 95-105 °C ot, 0.5 mm; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.25 (s, 6 H), 3.69 (s, 3 H), 6.82 (s, 2 H); ^{17}O NMR (CH_3CN) δ 16.11; IR (neat) 2820, 1375 cm^{-1}; MS *m/z* 150 (87.5), 135 (100), 91 (55.7).

2,6-Dimethyl-4-thiomethylanisole (4l). Methylation of 2,6-dimethyl-4-thiomethylphenol (16.80 g, 0.100 mol) according to the general procedure given for **11h** gave **4l**; Yield 16.26 g, 89%; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6 H), 2.44 (s, 6 H), 3.69 (s, 3 H), 6.94 (s, 2 H); ^{17}O NMR (CH_3CN) δ 16.9; IR (neat) 2830 cm^{-1}; MS *m/z* 182 (85.1), 167 (100).

Methyl 3,5-Di-*t*-butyl-4-methoxybenzoate (11c). 3,5-Di-*t*-butyl-4-hydroxybenzoic acid (75.0 g, 0.30 mol) was methylated according to the procedure given for **11h** except that twice as much dimethyl sulfate was added (85.2 mL, 0.90 mol). The yield was 79.9 g, 96%; mp 63-64 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18 H), 3.71 (s, 3 H), 3.89 (s, 3 H), 7.95 (s, 2 H); ^{17}O NMR (CH_3CN) δ 31.8 (OMe at C_4), 129.5 (CO<u>O</u>Me), 336.2 (C=O); IR (CCl_4) 2885, 1725, 1365 cm^{-1}; MS *m/z* 278 (30.1), 263 (100), 191 (20.7).

3,5-Di-*t*-butyl-4-methoxybenzylalcohol (11d). Under a nitrogen atm, ester **11c** (34.75 g, 0.125 mol), dissolved in ether (50 mL), was slowly added (35 min) to a solution of $LiAlH_4$ (3.104 g) in ether (50 mL) and the mixture was heated at reflux for 1 h. The reaction mixture was cooled and EtOAc (50 mL) was added dropwise. The mixture was poured cautiously onto ice water and shaken with ether (3 x 100 mL). The ether layers were combined, washed (H_2O, NaCl), dried ($MgSO_4$), filtered and concd (rotary evaporator) to yield **11d** (30.59 g, 98%); mp 101-102 °C (pet ether); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18 H), 2.15 (bs, 1 H), 3.67 (s, 3 H), 4.58 (s, 2 H), 7.24 (s, 2 H); ^{17}O NMR (CH_3CN) δ 5.7 (CH_2OH), 26.3 (OMe); IR (CCl_4) 3620 sharp, 2885, 1365 cm^{-1}; MS *m/z* 250 (50.4), 235 (100).

3,5-Di-*t*-butyl-4-methoxybenzaldehyde (11e). Alcohol **11d** (26.6 g, 0.106 mol) in CH_2Cl_2 (500 mL) was added to a magnetically stirred flask containing PCC (32.34 g, 0.150 mol) in CH_2Cl_2 (200 mL). After the addition the solution turned black and began to reflux. After stirring the solution for 1.5 h,

ether was added, decanted (3 x 100 mL), filtered through Dicalite and concd (rotary evaporator). The residue was passed through neutral alumina (50 g, ether) to give a thick oil (23.69 g, 90%) which crystallized upon Kugelrohr distillation (145-160 °C ot, 2.5 mm). The yield was 22.12 g, 84%; mp 55-57 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 18 H), 3.74 (s, 3 H), 7.80 (s, 2 H), 9.92 (s, 1 H); ^{17}O NMR (CH_3CN) δ 36.9 (OMe at C_4), 552.9 (C=O); IR (neat) 2825, 2725, 1700 cm^{-1}; MS *m/z* 248 (39.9), 233 (100), 161 (22.9).

3,5-Di-*t*-butyl-4-methoxybenzonitrile (11f). A warm solution of $NH_2OH{\cdot}HCl$ (5.88 g, 85 mmol) in H_2O (7 mL) was added to a magnetically stirred flask containing **11e** (17.36 g, 70 mmol) in 95% EtOH (28 mL). Sodium hydroxide (4.2 g in 5.6 mL H_2O) was added to give a cloudy solution. After stirring for 2 h, ice-H_2O (500 mL) was added and the mixture was filtered. The collected solid was dissolved in ether and dried ($MgSO_4$). Removal of the ether gave 17.94 g of crude oxime, mp 105-110 °C, which transferred to a 500 mL, round-bottomed flask and acetic anhydride (50 mL) was added. This mixture was heated at reflux for 30 min, cooled, and added to ice-water (200 mL). The beige solid was collected on filter paper and passed through alumina (25 g basic / 25 g neutral) with petroleum ether to yield **11f** (15.57 g, 91%); mp 73-75 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18 H), 3.72 (s, 3 H), 7.54 (s, 2 H); ^{17}O NMR (CH_3CN) δ 35.8; IR (CCl_4) 2890, 2250, 1370 cm^{-1}; MS *m/z* 245 (37.1), 230 (100), 158 (21.5).

4-Bromo-2,6-di-*t*-butylanisole (11g). Bromine (10.5 g, 66 mmol) was added to a magnetically stirred solution of 2,6-di-*t*-butylanisole (**11a**) (11.0 g, 50 mmol) in acetic acid (150 mL). After 1 h, the mixture was poured onto 500 mL of ice water, and shaken with ether (4 x 100 mL). The ether layer was washed with solutions of $NaHSO_3$, $NaHCO_3$, NaCl, dried ($MgSO_4$), filtered and concd (rotary evaporator) to give 5.81 g of a yellow oil which was distilled

(Kugelrohr 100-115 °C ot, 0.35 mm) and passed through neutral alumina with petroleum ether to give **11g** (5.58 g, 37%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18 H), 3.67 (s, 3 H), 7.33 (s, 2 H); ^{17}O NMR (CH_3CN) δ 28.9; IR (neat) 2875, 1570, 1370 cm^{-1}; MS *m/z* 300 (85.2), 298 (93.8), 285 (100), 283 (94.3).

2,6-Di-*t*-butyl-4-methoxyanisole (11h). 2,6-Di-*t*-butyl-4-methoxyanisole (9.44 g, 40 mmol) was methylated according to the general procedure given by McKillop.[51] After workup the resulting yellow oil was passed through acidic and basic alumina, and concd (rotary evaporator) to give **11h** (8.99 g, 90%); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 6.80 (s, 2 H); ^{17}O NMR (CH_3CN) δ 22.9 (OMe at C_1), 42.2 (OMe at C_4); IR (neat) 2840, 1370 cm^{-1}; MS *m/z* 250 (100), 235 (38.6), 220 (10.8), 179 (31.3).

2,6-Di-*t*-butyl-4-methylanisole (11i). Methylation of 2,6-di-*t*-butyl-4-methylphenol according to the procedure given for **11h** gave **11i** in 96% yield; bp 82-90 °C ot, 0.35 mm; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 18 H), 2.28 (s, 3 H), 3.67 (s, 3 H), 7.04 (s, 2 H); ^{17}O NMR (CH_3CN) δ 26.6; IR (neat) 2875, 1370 cm^{-1}; MS *m/z* 234.

2,6-Di-*t*-butyl-4-ethylanisole (11j). Methylation of 2,6-di-*t*-butyl-4-ethylphenol (11.7 g, 50 mmol) according to the procedure given for **11h** gave **11j** (11.4 g) in 92% yield; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.8 Hz), 1.43 (s, 18 H), 2.58 (q, 2 H, J = 7.8 Hz), 3.68 (s, 3 H), 7.07 (s, 2 H); ^{17}O NMR (CH_3CN) δ 26.9; IR (neat) 2885, 1365 cm^{-1}; MS *m/z* 248.

2,4,6-Tri-*t*-butylanisole (11k). Methylation of 2,4,6-tri-*t*-butylphenol (13.1 g, 50 mmol) according to the procedure given for **11h** gave **11i** (13.3 g) in 96% yield; mp °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9 H), 1.44 (s, 18 H), 3.68 (s, 3 H), 7.25 (s, 2 H); ^{17}O NMR (CH_3CN) δ 25.8; MS *m/z* 278, 263 (100)

1,2,3-Trimethoxybenzene (13a).[52] ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 9 H), 6.58 (d, 2 H), 6.99 (t, 1 H); ^{17}O NMR (CH_3CN) δ 1.6 (OMe at C_2), 36.1 (OMe at $C_{1,3}$).

3,4,5-Trimethoxyphenol (13b).[52] ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 6 H), 3.78 (s, 3 H), 6.09 (s, 2 H), 6.12 (s, 1 H); ^{17}O NMR (CH_3CN) δ -4.3 (OMe at C_4), 37.4 (OMe at $C_{3,5}$), 75.8 (OH).

1,2,3,5-Tetramethoxybenzene (13c). Methylation of 3,4,5-trimethoxyphenol (**13b**, 9.20 g, 50 mmol) according to the general procedure given **11h** gave **13c** (9.00 g) in 91% yield; mp 38-39 °C; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3 H), 3.79 (s, 3 H), 3.85 (s, 6 H), 6.16 (s, 2 H); ^{17}O NMR (CH_3CN) δ -3.0 (OMe at C_2), 36.6 (OMe at $C_{1,3}$), 44.6 (OMe at C_5); MS *m/z* 198.

3,4,5-Trimethoxytoluene (13d).[52] ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 3.82 (s, 3 H), 3.84 (s, 6 H), 6.39 (s, 2 H); ^{17}O NMR (CH_3CN) δ -1.0 (OMe at C_4), 35.2 (OMe at $C_{3,5}$).

3,4,5-Trimethoxyaniline (13e).[52] ^{1}H NMR ($CDCl_3$) δ 3.51 (bs, 2 H), 3.76 (s, 2 H), 3.80 (s, 6 H), 5.93 (s, 2 H); ^{17}O NMR (CH_3CN) δ -6.3 (OMe at C_4), 35.4 (OMe at $C_{3,5}$).

3,4,5-Trimethoxybenzylalcohol (13f).[52] ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 6H), 3.55 (s, 3H), 4.16 (bs, 1H), 4.30 (s, 2H), 6.33 (s, 2H); ^{17}O NMR (CH_3CN) δ 1.0 (OMe at C_4), 5.8 (CH_2OH), 36.4 (OMe at $C_{3,5}$).

3,4,5-Trimethoxyphenylacetonitrile (13g).[52] ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 2H), 3.84 (s, 3H), 3.86 (s, 6H), 6.54 (s, 2H); ^{17}O NMR (CH_3CN) δ 1.7 (OMe at C_4), 38.3 (OMe at $C_{3,5}$).

3,4,5-Trimethoxybenzoic acid (13h).[52] ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 6 H), 3.94 (s, 3 H), 7.39 (s, 2 H), 11.97 (s, 1 H); ^{17}O NMR (CH_3CN) δ 9.3 (OMe at C_4), 39.2 (OMe at $C_{3,5}$), 247.1 (CO_2H).

3,4,5-Trimethoxybenzonitrile (13i).[52] ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 6 H), 3.91 (s, 3 H), 6.87 (s, 2 H); ^{17}O NMR (CH_3CN) δ 12.9 (OMe at C_4), 41.7 (OMe at $C_{3,5}$).

3,4,5-Trimethoxybenzaldehyde (13j).[52] ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 6 H), 3.95 (s, 3 H), 7.14 (s, 2 H), 9.87 (s, 1 H); ^{17}O NMR (CH_3CN) δ 13.2 (OMe at C_4), 40.2 (OMe at $C_{3,5}$), 554.8 (C=O).

3,4,5-Trimethoxyacetophenone (13k).[52] ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 3.85 (s, 9H), 7.22 (s, 2H); ^{17}O NMR (CH_3CN) δ 8.7 (OMe at C_4), 37.8 (OMe at $C_{3,5}$), 544.6 (C=O).

CHAPTER III

USE OF ^{13}C NMR ANALYSIS IN THE STRUCTURAL ASSIGNMENT OF NATURAL PRODUCTS CONTAINING CROWDED AROMATIC METHOXY GROUPS. APPLICATION TO THE STRUCTURES OF MEDITERRANEOL A AND B

Introduction

Methoxy groups crowded by two ortho neighbors on an aromatic ring were previously reported[26,32,33] to show 4-9 ppm deshielding of the methoxy methyl signal in the ^{13}C NMR spectrum as compared to methoxy groups in anisoles flanked by only one or no such ortho neighbors. This deshielding was attributed to increased electron density on the crowded methoxy oxygen which in turn decreases the electron density on the methoxy carbon, causing a downfield shift of the ^{13}C NMR signal. The abnormally high electron density on the crowded methoxy oxygen was suggested, on the basis of PRDDO MO calculations and by ^{13}C NMR T_1 values (spin-lattice relaxation), to be the result of sterically induced loss of normal interaction of the nonbonding *p* orbitals of the methoxy oxygen with the π system of the aromatic ring.[32,33] Later, ^{17}O NMR studies showed, as expected, pronounced shielding of the methoxy oxygen signal if two ortho neighbors were present.[35]

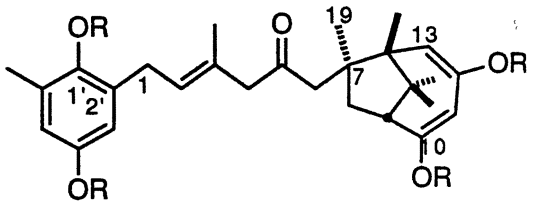
This separation of ^{13}C NMR chemical-shift values of crowded methoxy groups (59-64 ppm) from the uncrowded ones (55-57 ppm) in anisoles has persisted without exception in all anisoles examined by us and in all literature examples of proven structure.[1,8,29,31,34,53,54] Schuster et al. recently confirmed our earlier observations about ^{13}C and ^{17}O NMR chemical shifts of crowded anisoles and provided a correlation showing the influence of resonance contribution on the para carbon of anisoles.[29]

As additional ^{13}C and ^{17}O NMR data of crowded anisoles became known to us,[8,34,54] it was apparent that the ^{13}C NMR chemical shift of crowded methoxy groups would provide a convenient and definitive test of structure assignment of anisoles. Since there are numerous naturally occurring phenols which on methylation would provide crowded methoxy groups, the ^{13}C NMR chemical shift of methoxy carbons seemed worthy of further investigation as a tool in structure elucidation.

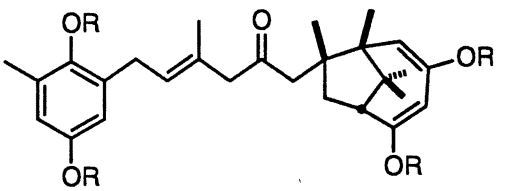
Results and Discussion

From ^{13}C NMR data of crowded methoxy groups in anisoles, it was concluded that the structures of methylated mediterraneol A and B (**26a** and **26b,** R = Me) were not consistent in the aromatic portion with the ^{13}C NMR data reported.[54] The structures of mediterraneol A and B (**26a** and **26b**, R = H), isolated from the brown alga *Cystoseira mediterranae,*[55] differ only in the orientation of the C-19 methyl group attached at C-7. Their structure derivation[55] was based primarily on the conversion to **26a** and **26b**, R = Me, and a subsequent intensive ^{1}H and ^{13}C NMR study. Silver oxide oxidation of mediterraneol B (**26b**, R = H) to a *p*-benzoquinone provided an important bit of structural evidence in the original assignment, since this suggested 1,4-location

of the oxygen functionalities and limited the isomeric substitution possibilities on the aromatic portion. Further, the model structure **32a** was proposed as representative of the *O*-methylated hydroquinone moiety and the first isoprene unit of mediterraneol A and B.[56] While extensive NMR data were provided for mediterraneol A and B methyl ethers, no NMR data for the model compound **32a** were included. Since all ^{13}C NMR methoxy signals reported for mediterraneol A and B were in the 55-57 ppm range, we suspected, as stated above, that the structures of their methyl ethers were in error in regard to substitution on the aromatic ring.



26a R = H or Me



26b R = H or Me

Since the model compound **32a** was not available and there was no evidence on influence of an alkenyl side chain on the ^{13}C NMR chemical shift of the crowded methoxy group, a synthesis of **32a** and related structures, as an extension of earlier work on such anisoles, was initiated to provide a group of reference compounds that would deny or support the original structure assignments to **26a** and **26b**.[55]

The ^{13}C NMR chemical-shift data in Table XIII (p 49) show that all crowded methoxy groups in the starting materials and products of the reactions

in Figures 11 and 12 (pp 47-48) exhibit a downfield chemical shift to the 60-64 ppm range. These model structures show that this shift persists despite variation of functions on the ortho side chain. Placement of functions [formyl (**27a-c**), carboxy (**28a-c**, **29a-c**), methoxycarbonyl (**30a-c**), hydroxy (**31a-c**, **35a**), keto (**34a**), and olefinic (**28a-c**, **32a-c**, **33a-c**, **36a**)] along the ortho side chain influences the individual shift values but does not cause the chemical shift to fall outside the observed range of 60-64 ppm. Also, 1-substituted 3,4,5-trimethoxybenzenes (**27d**, **28d**, **29d**, **30d**, **31d**, **32d**, and **33d**), where the changes (para to the crowded methoxy group) are only electronic, give a signal between 60-61 ppm for the crowded methoxy carbon.

The same functional variations in the side chain ortho to a noncrowded methoxy group [formyl (**27e**), carboxy (**28e**, **29e**), methoxycarbonyl (**30e**), hydroxy (**31e**, **35b**), keto (**34b**), and olefinic (**28e**, **32e**, **33e**, **36b**, **37**: Figure13, p 48)] did not shift the signal out of the 55-57 ppm range. While exceptions, involving other functional groups and geometric shapes, may eventually appear we feel, as stated earlier, that the examples presented in this report and others[57, 58] adequately support the claim that *^{13}C NMR deshielding of crowded aromatically bound methoxy groups can be used as a reliable predictive tool to support or deny structure assignment,* particularly in *O*-methylated naturally occurring phenolic materials, their synthetic intermediates, or degradation products.

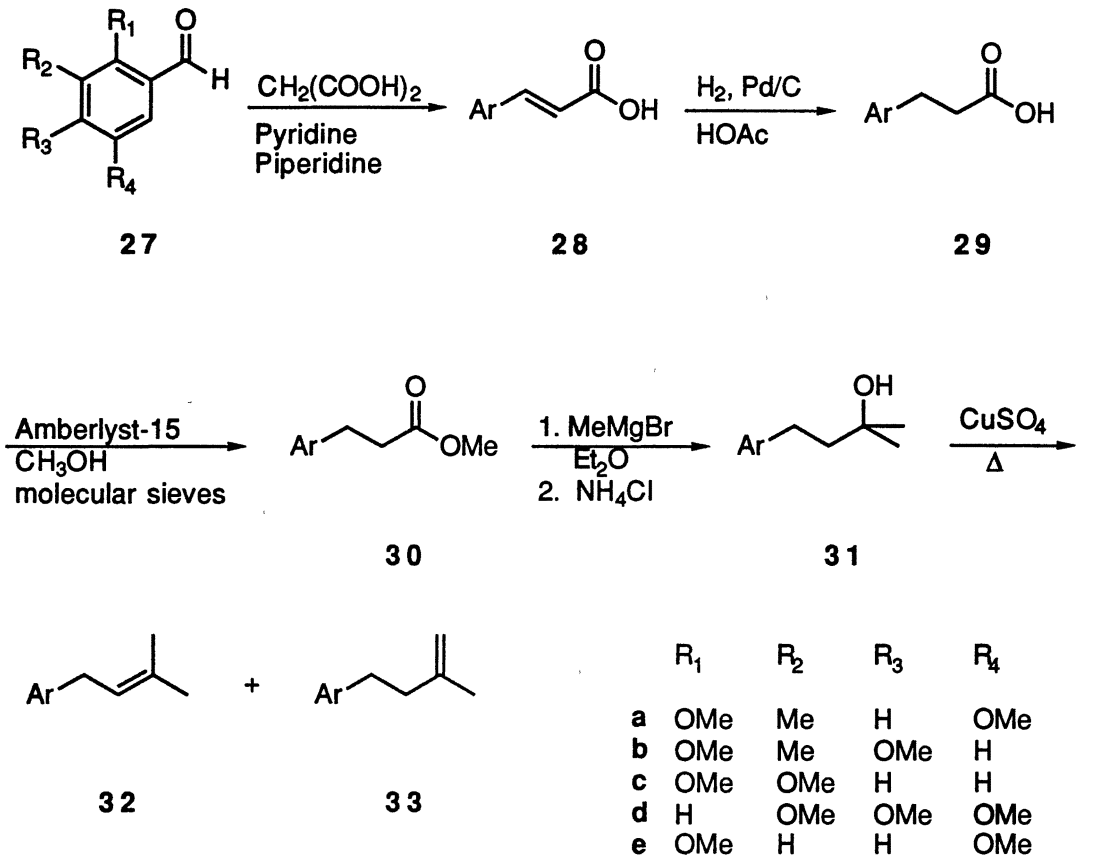


Figure 11. Reaction scheme for the synthesis of compounds in series **28-33**.

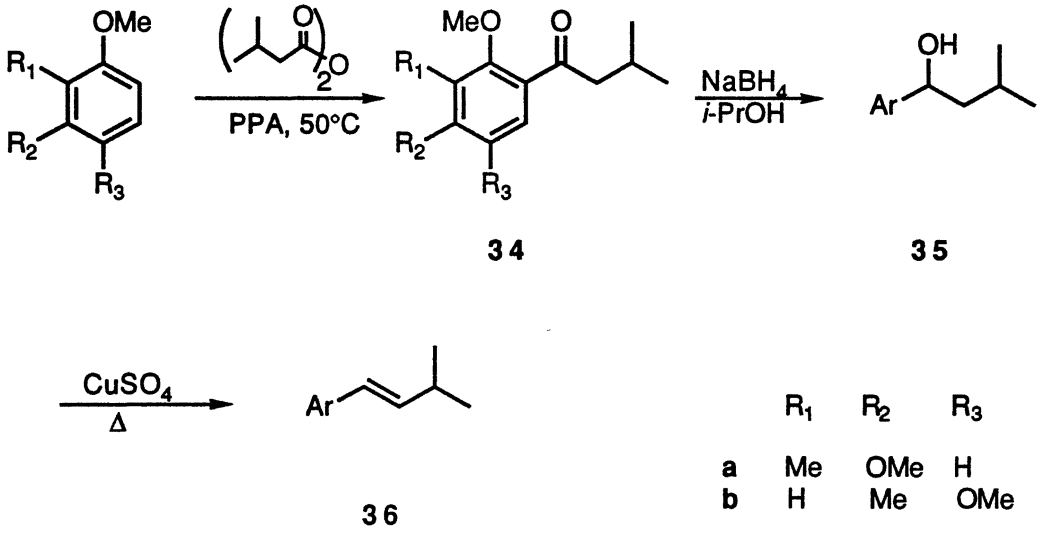


Figure 12. Reaction scheme for the synthesis of compounds in series **34-36**.

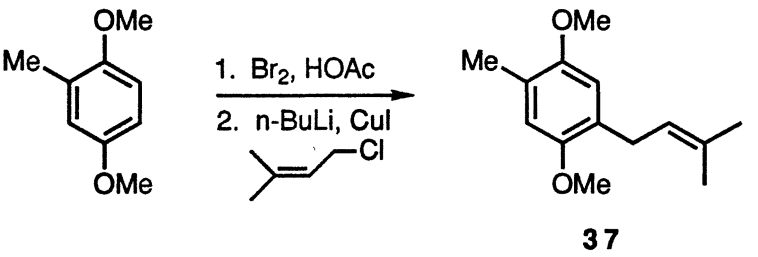


Figure 13. Reaction scheme for the synthesis of compound **37.**

Table XIII. ^{13}C NMR Chemical Shift Values of Crowded[a] Methoxy Groups for Compounds in Figures 11 and 12.

compd	a	b	c	d
27	63.5	63.2	62.3	61.0
28	61.8	61.6	61.4	61.0
29	60.6	60.6	60.2	60.8
30	60.6	60.6	60.5	60.7
31	60.7	60.7	60.6	60.9
32	60.5	60.5	60.6	60.8
33	60.6	60.7	60.5	60.9
34	62.1			
35	61.3			
36	60.6			

[a] As shown in the experimental section for chapter III (p 50), uncrowded methoxy groups show ^{13}C NMR resonances in the range of 55-57 ppm.

Experimental Section for Chapter III

General Experimental Details: See page 35, Chapter II.

2,5-Dimethoxy-3-methylbenzaldehyde (27a).[59] ^{1}H NMR δ 2.32 (s, 3 H), 3.84 (s, 3 H), 7.02 (s, 1 H), 7.15 (s, 1 H), 10.36 (s, 1 H); ^{13}C NMR δ 15.59, 55.65, 63.50, 107.54, 125.11, 129.35, 133.71, 155.83, 156.42, 190.12.

2,4-Dimethoxy-3-methylbenzaldehyde (27b).[52] ^{13}C NMR δ 8.52, 55.90, 63.19, 106.55, 120.14, 122.83, 127.96, 162.60, 164.01, 189.19.

2,3-Dimethoxybenzaldehyde (27c).[52] ^{13}C NMR δ 56.03, 62.32, 118.14, 119.10, 124.16, 129.77, 152.70, 153.04, 190.11.

3,4,5-Trimethoxybenzaldehyde (27d).[52] ^{13}C NMR δ 56.27, 60.99, 106.71, 131.74, 143.59, 153.65, 191.06.

2,5-Dimethoxybenzaldehyde (27e).[52] ^{13}C NMR δ 55.80, 56.16, 110.48, 113.37, 123.42, 124.96, 153.62, 156.71, 189.52.

2,5-Dimethoxy-3-methylcinnamic acid (28a).[59,60] Compound **27a** (10.80 g, 60 mmol) was reacted with malonic acid (12.5 g, 123 mmol) in pyridine (25 mL) and piperidine (1 mL) to yield **28a** (12.10 g, 91%); mp 164-166 °C, lit[59] 166-167 °C; ^{1}H NMR δ 2.30 (s, 3 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 6.47 (d, 1 H, J = 15.9 Hz), 6.82 (d, 1 H, J = 3.0 Hz), 6.92 (d, 1 H, J = 3.0 Hz), 8.06 (d, 1 H, J = 16.2 Hz); ^{13}C NMR δ 16.18, 55.57, 61.81, 109.06, 118.14, 119.98, 127.79, 133.12, 142.17, 152.24, 155.62, 171.94.

2,4-Dimethoxy-3-methylcinnamic acid (28b). Prepared by the procedure given for **28a**, yield 98%; mp 192-194 °C; ^{1}H NMR δ 2.17 (s, 3 H), 3.75 (s, 3 H), 3.87 (s, 3 H), 6.42 (d, 1 H, J = 16.2 Hz), 6.69 (d, 1 H, J = 8.7 Hz), 7.45 (d, 1 H, J = 8.7 Hz), 8.02 (d, 1 H, J = 15.9 Hz); ^{13}C NMR δ 8.91, 55.75, 61.61, 106.60, 115.30, 120.33, 126.43, 142.43, 159.00, 161.05, 172.04; HRMS calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0893.

2,3-Dimethoxycinnamic acid (28c).[52] ^{13}C NMR δ 55.9, 61.4, 114.3, 118.6, 119.4, 124.3, 128.2, 148.7, 153.1, 172.3.

3,4,5-Trimethoxycinnamic acid (28d).[52] ^{13}C NMR δ 56.18, 60.99, 105.57, 116.52, 129.50, 140.55, 147.08, 153.47, 172.51.

2,5-Dimethoxycinnamic acid (28e).[52] ^{13}C NMR δ 55.78, 56.05, 112.47, 113.39, 117.75, 117.93, 123.49, 142.21, 153.05, 153.46, 173.03.

3-(2,5-Dimethoxy-3-methylphenyl)-propionic acid (29a). The cinnamic acid **28a** (11.00 g, 50 mmol) was hydrogenated for 3 h at 50 psi in the presence of 5% Pd/C (1 g) and HOAc (200 mL) in a Paar shaker. The reaction mixture was filtered through Dicalite, which was washed several times with HOAc, and concd (rotary evaporator) to give **29a** (10.97 g, 99%); mp 89-90 °C (hexane / $CHCl_3$), lit[59] 87.5-88.5 °C; ^1H NMR δ 2.27 (s, 3 H), 2.69 (t, 2 H, J = 7.5 Hz), 2.94 (t, 2 H, J = 7.5 Hz), 3.70 (s, 3 H), 3.74 (s, 3 H), 6.57 (s, 1 H), 6.59 (s, 1 H); ^{13}C NMR δ 16.43, 25.51, 34.69, 55.41, 60.59, 112.54, 114.53, 132.09, 133.84, 150.58, 155.51, 179.36.

Compounds **29b**, **29c**, and **29e** were prepared by the procedure given for **29a**.

3-(2,4-Dimethoxy-3-methylphenyl)-propionic acid (29b). Yield 98%; mp 80-81 °C (hexane / $CHCl_3$), lit[61] 54-56 °C; ^1H NMR δ 2.15 (s, 3 H), 2.66 (t, 2 H, J = 7.8 Hz), 2.91 (t, 2 H, J = 7.8 Hz), 3.72 (s, 3 H), 3.80 (s, 3 H), 6.58 (d, 2 H, J = 8.4 Hz), 6.98 (d, 2 H, J = 8.4 Hz); ^{13}C NMR δ 9.21, 25.07, 35.02, 55.63, 60.63, 106.09, 119.80, 125.14, 126.73, 157.34, 157.55, 179.74; HRMS calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1051.

3-(2,3-Dimethoxyphenyl)propionic acid (29c). Yield 96%; mp 67-68 °C, lit[62] 69-70 °C; ^{13}C NMR δ 25.11, 34.51, 55.40, 60.24, 110.67, 121.35, 123.63, 133.58, 146.79, 152.34, 179.02.

3-(3,4,5-Trimethoxyphenyl)propionic acid (29d).[52] ^{13}C NMR δ 31.04, 35.80, 56.07, 60.83, 105.33, 135.98, 136.56, 153.26, 178.92.

3-(2,5-Dimethoxyphenyl)-propionic acid (29e). Yield: 95%; mp 63-65 °C, lit[63] 66-67 °C; ^{13}C NMR δ 26.01, 33.99, 55.68, 55.68, 111.01, 111.67, 116.36, 129.66, 151.74, 153.39, 179.64.

Methyl 3-(2,5-Dimethoxy-3-methylphenyl)-propionate (30a).[64] In a 500-mL round-bottom flask, fitted with a Soxhlet extractor containing molecular sieves (70 g), was placed **29a** (10.57 g, 47 mmol), methanol (150 mL) and Amberlyst-15 (1.10 g). The molecular sieves were covered with methanol and the mixture was heated at reflux for 48 h with magnetic stirring. The solution was cooled, filtered through Dicalite, and concentrated under vacuum. The concentrate was transferred to a separatory funnel with ether (100 mL), washed ($NaHCO_3$, NaCl) and dried ($MgSO_4$). Removal of the ether and Kugelrohr distillation afforded **30a** (10.01 g, 89%). IR (neat) 1730 cm^{-1} (C=O); ^1H NMR δ 2.27 (s, 3 H), 2.62 (t, 2 H, J = 8.0 Hz), 2.93 (t, 2 H, J = 8.0 Hz), 3.68 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 6.56 (d, 1 H, J = 3.0 Hz), 6.58 (d, 1 H, J = 3.0 Hz); ^{13}C NMR δ 16.42, 25.75, 34.77, 51.60, 55.38, 60.59, 112.52, 114.39, 132.01, 134.14, 150.58, 155.49, 173.58; HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1209.

Compounds **30b-30e** were prepared by the procedure given for **30a**.

Methyl 3-(2,4-Dimethoxy-3-methylphenyl)-propionate (30b). Yield 93%; IR (neat) 1730 cm^{-1} (C=O); ^1H NMR δ 2.15 (s, 3 H), 2.61 (t, 2 H, J = 8.4 Hz), 2.91 (t, 2 H, J = 8.4 Hz), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 6.57 (d, 1 H, J = 8.4 Hz), 6.97 (d, 1 H, J = 8.4 Hz); ^{13}C NMR δ 9.20, 25.35, 35.05, 51.54, 55.57, 60.62, 106.01, 119.75, 125.44, 126.74, 157.38, 157.48, 173.77; HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1204.

Methyl 3-(2,3-Dimethoxyphenyl)-propionate (30c)[65] Yield 95%; IR (neat) 1730 cm^{-1} (C=O); ^1H NMR δ 2.61 (t, 2 H, J = 9 Hz), 2.88 (t, 2 H, J = 9 Hz), 3.66 (s, 3 H), 3.84 (s, 6 H), 6.76-6.82 (m, 2 H), 6.95 (t, 1 H, J = 7 Hz); ^{13}C NMR δ 25.65, 34.75, 51.46, 55.63, 60.50, 110.85, 121.74, 123.91, 134.25, 147.23, 152.76, 173.49.

Methyl 3-(3,4,5-Trimethoxyphenyl)-propionate (30d).[66] Yield 91%; ^{13}C NMR δ 31.34, 35.78, 51.50, 55.98, 60.65, 105.35, 136.46, 136.52, 153.27, 173.19.

Methyl 3-(2,5-Dimethoxyphenyl)-propionate (30e).[67] Yield 61%; IR (neat) 1730 cm^{-1} (C=O); ^1H NMR δ 2.59 (t, 2 H, J = 7.5 Hz), 2.90 (t, 2 H, J = 7.5 Hz), 3.65 (s, 3 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 6.66-6.78 (m, 3 H); ^{13}C NMR δ 26.31, 34.04, 51.33, 55.43, 55.62, 111.15, 111.51, 116.42, 130.05, 151.81, 153.65, 173.49.

4-(2,5-Dimethoxy-3-methylphenyl)-2-methyl-2-butanol (31a).[68] In a dry 500-mL metal flask fitted with a reflux condenser and dropping funnel, was added **30a** (9.37 g, 39 mmol) and anhyd ether (60 mL). With nitrogen flow, excess methylmagnesium bromide (Aldrich, 3 M, 56 mL, 168 mmol) was added dropwise for 10 min and the reaction was heated at reflux for 1 h with magnetic stirring. After cooling, the reaction mixture was treated with a saturated NH_4Cl solution, extracted with ether, dried ($MgSO_4$), concd (rotary evaporator), and distilled (Kugelrohr) to give **31a** (9.02 g, 96%). IR (neat) 3650-3150 cm^{-1} (OH); ^{13}C NMR δ 16.43, 25.08, 29.26, 44.97, 55.41, 60.68, 70.84, 112.64, 113.88, 131.92, 136.27, 150.38, 155.55.

Compounds **31b-31e** were prepared by the procedure given for **31a**.

4-(2,4-Dimethoxy-3-methylphenyl)-2-methyl-2-butanol (31b). Yield 89%; IR (neat) 3650-3150 cm^{-1} (OH); ^1H NMR δ 1.28 (s, 6 H), 1.58 (bs, 1 H), 1.75 (m, 2 H), 2.16 (s, 3 H), 2.66 (5 line m, 2 H), 3.73 (s, 3 H), 3.80 (s, 3 H),

6.61 (d, 1 H, J = 8.4 Hz), 6.97 (d, 1 H, J = 8.4 Hz); ^{13}C NMR δ 9.17, 24.54, 29.24, 45.25, 55.62, 60.67, 70.89, 106.20, 119.70, 126.76, 127.47, 157.05, 157.13; HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1570.

4-(2,3-Dimethoxyphenyl)-2-methyl-2-butanol (31c). Yield 93%; IR (neat) 3650-3150 cm^{-1} (OH); ^{1}H NMR δ 1.28 (s, 6 H), 1.75 (5 line m, 2 H), 1.84 (bs, 1 H), 2.71 (5 line m, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.78 (m, 2 H), 6.97 (m, 1 H); ^{13}C NMR δ 24.84, 29.16, 44.96, 55.67, 60.63, 70.84, 110.14, 121.79, 123.95, 136.54, 146.90, 152.74; HRMS calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1416.

2-Methyl-4-(3,4,5-trimethoxyphenyl)-2-butanol (31d).[69,70] Yield 92%; IR (neat) 3650-3150 cm^{-1} (OH); ^{13}C NMR δ 29.40, 31.16, 45.69, 56.05, 60.86, 70.84, 105.14, 136.00, 138.35, 153.14.

4-(2,5-Dimethoxyphenyl)-2-methyl-2-butanol (31e). Yield 92%; IR (neat) 3650-3100 cm^{-1} (OH); ^{1}H NMR δ 1.27 (s, 6 H), 1.74 (5 line m, 2 H), 1.98 (bs, 1 H), 2.67 (5 line m, 2 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 6.73 (m, 3 H); ^{13}C NMR δ 25.30, 29.18, 43.93, 55.64, 55.93, 70.95, 110.87, 111.26, 116.07, 132.26, 151.57, 153.54; HRMS calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1412.

1-(2,5-Dimethoxy-3-methylphenyl)-3-methyl-2-butene (32a).[71] The Kugelrohr distillation of **6a** (8.75 g, 37 mmol) and anhyd $CuSO_4$ (9.0 g) gave a mixture (1:1, determined from the ratio of the signals at 5.28 (**32a**) and 4.76 ppm (**33a**) in the ^{1}H NMR spectrum) of olefins **32a** and **33a** (7.66 g, 95%) which was separated on $AgNO_3$-impregnated silica gel (hexane / ethyl acetate). ^{1}H NMR δ 1.73 (d, 6 H, J = 1.5 Hz), 2.28 (s, 3 H), 3.33 (d, 2 H, J = 7.2 Hz), 3.68 (s, 3 H), 3.75 (s, 3 H), 5.28 (pt, 1 H, J = 7.5, 1.5 Hz), 6.55 (s, 2 H); ^{13}C NMR δ 16.42, 17.84, 25.77, 28.49, 55.38, 60.48, 112.78, 113.50, 122.91, 131.74, 132.55, 135.48, 150.36, 155.49; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1452.

Compounds **32b-e** and **33a-e** were prepared by the procedure given for **32a.**

1-(2,4-Dimethoxy-3-methylphenyl)-3-methyl-2-butene (32b). Ratio of **32b**:**33b**, 3:1; yield 91%; ^{1}H NMR δ 1.73 (s, 6 H), 2.16 (s, 3 H), 3.30 (d, 2 H, J = 6.9 Hz), 3.70 (s, 3 H), 3.79 (s, 3 H), 5.28 (pt, 1 H, J = 7.5, 1.5 Hz), 6.58 (d, 1 H, J = 8.4 Hz), 6.95 (d, 1 H, J = 8.4 Hz); ^{13}C NMR δ 9.15, 17.79, 25.78, 28.05, 55.58, 60.47, 106.08, 119.57, 123.58, 126.69, 131.91, 157.01, 157.06; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1562.

1-(2,3-Dimethoxyphenyl)-3-methyl-2-butene (32c). Ratio of **32c**:**33c**, 2:1; yield 98%; ^{1}H NMR δ 1.73 (s, 6 H), 3.35 (d, 2 H, J = 7.2 Hz), 3.81 (s, 3 H), 3.85 (s, 3 H), 5.28 (pt, 1 H, J = 7.5, 1.5 Hz), 6.78 (m, 2 H), 6.98 (m, 1 H); ^{13}C NMR δ 22.59, 28.36, 38.88, 55.63, 60.62, 109.99, 110.11, 121.79, 123.74, 136.07, 145.71, 147.08, 152.71; HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1307.

3-Methyl-1-(3,4,5-trimethoxyphenyl)-2-butene (32d).[69] Ratio of **32d**:**33d**, 4:1; yield 95%; ^{1}H NMR δ 1.72 (s, 3 H), 1.76 (s, 3 H), 3.29 (d, 2 H, J = 7.2 Hz), 3.82 (s, 3 H), 3.85 (s, 6 H), 5.32 (pt, 1 H, J = 7.5, 1.5 Hz), 6.40 (s, 2 H); ^{13}C NMR δ 17.87, 25.77, 34.68, 56.03, 60.84, 103.57, 105.14, 123.04, 132.77, 137.61, 153.13.

1-(2,5-Dimethoxyphenyl)-3-methyl-2-butene (32e).[72] Ratio of **32e**:**33e**, 2:1; yield 95%; ^{13}C NMR δ 17.75, 25.82, 28.47, 55.62, 56.01, 110.44, 111.14, 116.01, 122.27, 131.47, 132.74, 151.62, 153.57.

4-(2,5-Dimethoxy-3-methylphenyl)-2-methyl-1-butene (33a). ^{1}H NMR δ 1.79 (s, 3 H), 2.28 (s, 3 H), 2.29 (m, 2 H), 2.74 (m, 2 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 4.76 (s, 2 H), 6.57 (s, 2 H); ^{13}C NMR δ 16.46, 22.62, 28.54, 38.85, 55.35, 60.64, 110.03, 112.61, 113.76, 131.78, 135.86, 145.68, 150.49, 155.43; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1479.

4-(2,4-Dimethoxy-3-methylphenyl)-2-methyl-1-butene (33b). ^{1}H NMR δ 1.79 (s, 3 H), 2.16 (s, 3 H), 2.28 (t, 2 H, J = 9.0 Hz), 2.72 (t, 2 H, J = 8.4 Hz), 3.72 (s, 3 H), 3.80 (s, 3 H), 4.75 (s, 2 H), 6.58 (d, 1 H, J = 8.4 Hz), 6.98 (d, 1 H, J = 8.4 Hz); ^{13}C NMR δ 9.19, 22.64, 28.07, 39.13, 55.57, 60.65, 105.99, 109.88, 119.54, 126.68, 127.12, 145.93, 157.01, 157.22; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1467.

4-(2,3-Dimethoxyphenyl)-2-methyl-1-butene (33c). ^{1}H NMR δ 1.79 (s, 3 H), 2.29 (t, 2 H, J = 8.1 Hz), 2.77 (t, 2 H, J = 7.8 Hz), 3.83 (s, 3 H), 3.84 (s, 3 H), 4.74 (s, 2 H), 6.78 (m, 2 H), 6.97 (m, 1 H); ^{13}C NMR δ 17.80, 25.78, 28.41, 55.68, 60.47, 110.08, 121.69, 123.01, 123.85, 132.20, 135.72, 146.94, 152.77; HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1293.

2-Methyl-4-(3,4,5-trimethoxyphenyl)-1-butene (33d).[69] ^{1}H NMR δ 1.78 (s, 3 H), 2.31 (t, 2 H, J = 8.7 Hz), 2.70 (t, 2 H, J = 8.4 Hz), 3.83 (s, 3 H), 3.85 (s, 6 H), 4.76 (d, 2 H, J = 6.0 Hz), 6.42 (s, 2 H); ^{13}C NMR δ 22.65, 34.68, 39.64, 56.04, 60.85, 105.17, 110.22, 136.05, 138.05, 145.32, 153.06.

4-(2,5-Dimethoxyphenyl)-2-methyl-1-butene (33e). ^{1}H NMR δ 1.77 (s, 3 H), 2.27 (t, 2 H, J = 8.1 Hz), 2.73 (t, 2 H, J = 8.1 Hz), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.72 (s, 3 H), 6.72 (m, 3 H); ^{13}C NMR δ 22.62, 28.78, 37.92, 55.62, 55.89, 109.86, 110.76, 111.14, 116.16, 131.93, 145.84, 151.76, 153.44; HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1312.

1-(2,4-Dimethoxy-3-methylphenyl)-3-methyl-1-butanone (34a). 2,6-Dimethoxytoluene (7.6 g, 50 mmol), PPA (85 g), and isovaleric anhydride (9.3 g, 50 mmol) were heated to 45 °C with efficient stirring for 1 h. After cooling the reaction mixture, ice was added slowly and the mixture was shaken with ether (3 x 75 mL). The ether layer was washed ($NaHCO_3$, NaCl) and dried ($MgSO_4$). The ether extract was concentrated (rotary evaporator) and the residue was passed through basic alumina (50 g) with low-boiling

petroleum ether to yield **34a** (10.55 g, 89%); IR (CCl_4) 1675 cm^{-1}; ^1H NMR δ 0.95 (d, 6 H, J = 6.0 Hz), 2.16 (s, 3 H), 2.22 (m, 1 H, J = 6.9 Hz), 2.84 (d, 2 H, J = 7.2 Hz), 3.73 (s, 3 H), 3.86 (s, 3 H), 6.67 (d, 1 H, J = 8.7 Hz), 7.49 (d, 1 H, J = 8.7 Hz); ^{13}C NMR δ 8.85, 22.71, 25.21, 51.44, 55.72, 62.05, 105.87, 120.20, 126.56, 128.39, 158.58, 161.61, 202.34; HRMS calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1402.

1-(2,5-Dimethoxy-4-methylphenyl)-3-methyl-1-butanone (34b). The procedure given for **34a** was used to prepare **34b** in 92% yield ; mp 46-47 °C, lit[73] 48-48.5 °C; ^{13}C NMR δ 16.65, 22.84, 25.10, 52.91, 55.62, 55.92, 111.00, 114.80, 125.94, 133.03, 151.75, 153.00, 201.28.

1-(2,4-Dimethoxy-3-methylphenyl)-3-methyl-1-butanol (35a). Ketone **34a** (7.08 g, 30 mmol) dissolved in 50 mL of isopropyl alcohol was added to a stirred solution of $NaBH_4$ (1.14 g) in isopropyl alcohol (50 mL). After 3 days, 5% HCl was added and the mixture was extracted with ether (3 x 75 mL). The ether layer was washed ($NaHCO_3$, NaCl), dried ($MgSO_4$), and concd (rotary evaporator) to give **35a** (6.67 g, 93%); IR (CCl_4) 3600-3100 cm^{-1}; ^1H NMR δ 0.97 (dd, 6 H, J = 6.3, 4.8 Hz), 1.52 (m, 1 H), 1.76 (m, 2 H), 2.15 (s, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 5.01 (m, 1 H), 6.65 (d, 1 H, J = 8.4 Hz), 7.19 (d, 1 H, J = 8.7 Hz); ^{13}C NMR δ 9.21, 22.09, 23.37, 25.03, 47.50, 55.61, 61.27, 67.33, 106.22, 119.49, 123.98, 130.03, 156.54, 158.05.

1-(2,5-Dimethoxy-4-methylphenyl)-3-methyl-1-butanol (35b). The procedure given for **35a** was used to prepare **35b** in 93%yield; IR (CCl_4) 3600-3100 cm^{-1}; ^1H NMR δ 0.94 (d, 6 H, J = 5.4 Hz), 1.49 (m, 1 H), 1.74 (m, 2 H), 2.20 (s, 3 H), 2.75 (bs, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.92 (dd, 1 H, J = 7.5, 1.5 Hz), 6.66 (s, 1 H), 6.83 (s, 1 H); ^{13}C NMR δ 16.20, 22.12, 23.37, 24.97, 47.02, 55.90, 55.95, 68.47, 109.29, 113.93, 125.73, 131.23, 149.97, 151.81; HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1572.

1-(2,4-Dimethoxy-3-methylphenyl)-3-methyl-1-butene (36a). The procedure given for **31a** was used to prepare **36a** in 85%yield; ^{1}H NMR δ 1.09 (d, 6 H, *J* = 6.9 Hz), 2.15 (s, 3 H), 2.47 (dh, 1 H, *J* = 6.9, 1.5 Hz), 3.69 (s, 3 H), 3.80 (s, 3 H), 6.07 (dd, 1 H, *J* = 15.9, 6.9 Hz), 6.55 (d, 1 H, *J* = 16.2 Hz), 6.60 (d, 1 H, *J* = 8.7 Hz), 7.25 (d, 1 H, *J* = 8.7 Hz); ^{13}C NMR δ 8.85, 22.66, 31.83, 55.62, 60.57, 106.38, 119.51, 121.48, 123.57, 124.04, 137.09, 156.36, 157.70; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1464.

1-(2,5-Dimethoxy-4-methylphenyl)-3-methyl-1-butene (36b). The procedure given for **31a** was used to prepare **36b** in 63%yield; ^{1}H NMR δ 1.10 (d, 6 H, *J* = 6.6 Hz), 2.20 (s, 3 H), 2.48 (dh, 1 H, *J* = 6.9, 1.5 Hz), 3.78 (s, 3 H), 3.81 (s, 3 H), 6.11 (dd, 1 H, *J* = 15.9, 6.9 Hz), 6.65 (d, 1 H, *J* = 15.0 Hz), 6.67 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR δ 16.29, 22.65, 31.91, 55.98, 56.41, 108.19, 114.64, 121.35, 124.73, 126.17, 137.52, 150.29, 151.93; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1470.

1-(2,5-Dimethoxy-4-methylphenyl)-3-methyl-2-butene (37). Bromine (20.7 g, 0.13 mol) was added dropwise to a solution of 2,5-dimethoxytoluene (15.2 g, 0.10 mol) in 300 mL of acetic acid over a 30 min period. The reaction mixture was magnetically stirred 1 h and poured onto 200 mL of ice. The crystallized product was filtered out and washed with saturated $NaHCO_3$. The collected off-white crystals were dissolved in 200 mL of $CHCl_3$, dried ($MgSO_4$), and concd (rotary evaporator) to yield 4-bromo-2,5-dimethoxytoluene (20.89 g, 90%, mp 88-90 °C). *n*-BuLi (2.5 M in hexane, 18 mL, 45 mmol) was added to an ice-cold solution of 4-bromo-2,5-dimethoxytoluene (9.24 g, 40 mmol) dissolved in 200 mL of dry ether. After 3 h of magnetic stirring, CuI (4.76 g, 25 mmol) was added in 3 portions and the mixture stirred 2 h. 1-Chloro-3-methyl-2-butene (4.7 g, 45 mmol) was added dropwise over 20 min and stirred 10 h. The mixture was poured on 300 mL of

ice, acidified with 10% HCl, and shaken with ether (3 x 75 mL). The ether extract was washed (NaCl), dried ($MgSO_4$), and concd (rotary evaporator) to give 9.25 g of a brown semi-solid. Kugelrohr distillation[74] and silica gel chromatography (hexane) yielded **37.** ^1H NMR δ 1.72 (d, 6 H, J = 3.9 Hz), 2.20 (s, 3 H), 3.29 (d, 2 H, J = 7.5 Hz), 3.77 (s, 6 H), 5.29 (pt, 1 H, J = 7.5, 1.5 Hz), 6.65 (s, 1 H), 6.67 (s, 1 H); ^{13}C NMR δ 16.10, 17.79, 25.81, 28.45, 56.10, 56.25, 112.41, 114.02, 122.88, 124.45, 128.03, 132.25, 150.96, 151.64; HRMS calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1483.

CHAPTER IV

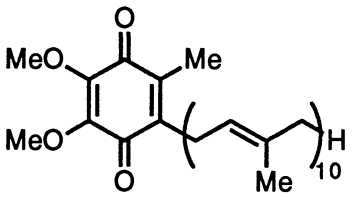
^{13}C AND ^{17}O NMR STUDIES ON THE METHOXY SUBSTITUENTS OF UBIQUINONE-10 AND RELATED 1,4-BENZOQUINONES

Introduction

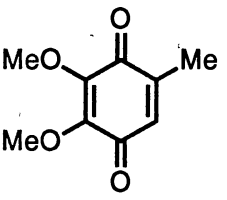
Crowded methoxy groups of anisoles have been shown to undergo 5-9 ppm deshielding in the ^{13}C NMR spectrum and significant shielding in the ^{17}O NMR spectrum as compared to noncrowded methoxy groups.[26,33,35] Crowded methoxy groups have an increased charge on the methoxy oxygen and are better complexing agents to acidic reagents.[39,43] The quinone portion of the ubiquinones (coenzymes $Q_{0\text{-}10}$) contains two such methoxy groups. These methoxy groups generally receive less attention than the quinone system and the polyene side chain in spectroscopic analysis. ^{13}C NMR studies of methoxy substituted quinones are not common, probably due to their limited supply from natural sources. However, even in synthetic studies of methoxy substituted quinones, ^{13}C NMR data are rarely reported.[75] Only a few articles have reported the ^{17}O NMR data for quinones and none of these has contained methoxy groups.[37,76] Increased usage of ^{13}C and ^{17}O NMR as a structural probe for natural and synthetic quinones is expected, as more sensitive NMR probes become available, thus allowing for lower sample concentrations.

Results and Discussion

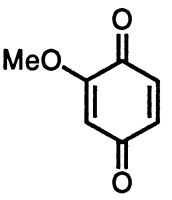
As a continuation of the application of NMR analysis of crowded methoxy groups attached to aromatic rings, the ^{13}C and ^{17}O NMR spectra of methoxy substituted 1,4-benzoquinones related to the ubiquinones were studied. In this study, the quinone carbonyl oxygen was considered to serve as an ortho substituent to the methoxy group and through crowding to influences the NMR signals. The compounds used in this study are shown below in Figure 14.



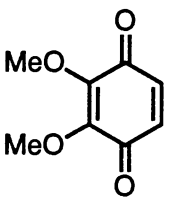
38



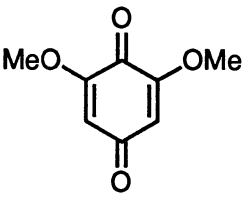
39



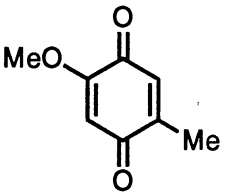
40



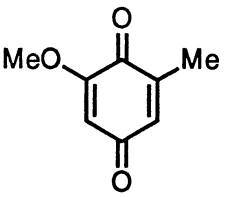
41



42



43



44

Figure 14. Structures of the methoxy-substituted quinones studied.

Quinones **38**, **39**, **42** and **43** were commercially available. Quinones (**40**, **41**, and **44**) were synthesized as shown in Figure 15. These reactions involve the oxidation of the corresponding phenols using Fremy's salt or dihydroquinones with CAN in acetonitrile to the give corresponding quinone.

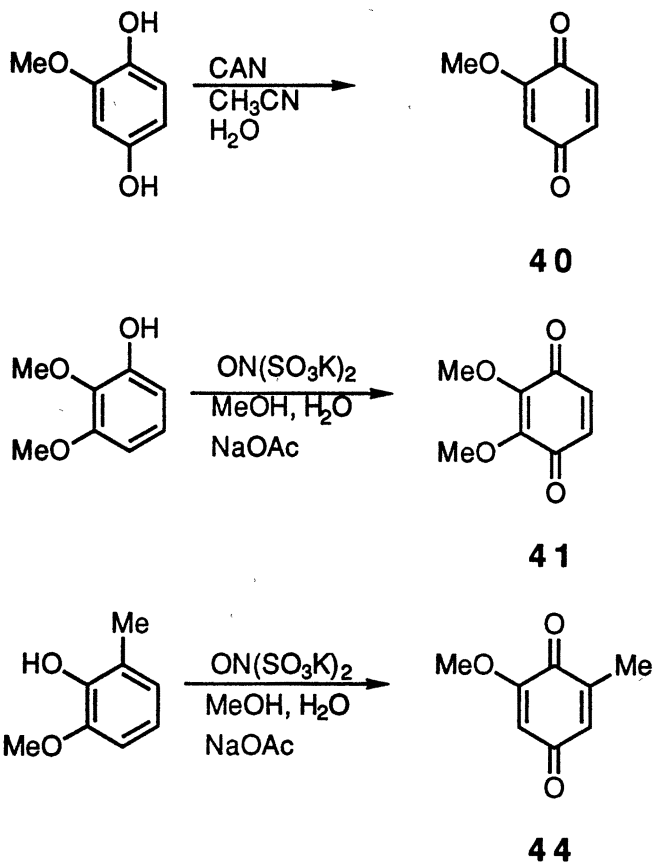


Figure 15. Reaction scheme for the synthesis of compounds **40**, **41**, and **44**.

The ^{13}C NMR spectra of compounds in Table XIV (p 64) show that the crowded methoxy groups have similar spectroscopic properties to the methoxy

groups in anisoles (i.e., crowded methoxy groups are deshielded compared to the noncrowded ones). The ^{13}C NMR signals for the noncrowded methoxy groups (**40**, **42-44**) are between 56.3-56.5 ppm, whereas the crowded methoxy groups (**38**, **39**, **41**) have signals appearing between 61.2-61.3 ppm. These data, along with previous X-ray data,[77] show that there is a distinction between the in-plane and out-of-plane methoxy groups in quinones.

Listed in Table XIV, are the ^{17}O NMR data of the methoxy substituted quinones (**39**, **40**, **41**, and **44**). The oxygen NMR spectrum of Coenzyme Q-10 was not obtained because of the limited solubility of the Co-Q_{10} in acetonitrile at 75 °C.

TABLE XIV. ^{13}C and ^{17}O NMR signals of the Methoxy Methyl and Carbonyl Groups of Quinones

	^{13}C NMR		^{17}O NMR	
compd	δ (OCH_3)	δ (C=O)	δ (OCH_3)	δ (C=O)
38	61.2	184.8 183.9	----------[a]	----------[a]
39	61.2 61.2	184.4 184.2	29.4	582.6 579.5
40	56.3	187.5 181.7	74.4	598.8
41	61.3	184.1	30.3	595.0
42	56.5	186.9 176.7		
43	56.3	187.7 182.1		
44	56.3	187.4 182.4	72.6	590.1 582.6

[a] No signal was observed after 24 h.

Experimental Section for Chapter IV

General Experimental Details. See page 35, Chapter II.

Coenzyme Q_{10} (38).[52] ^{1}H NMR δ 1.57 (s, 3H), 1.60 (s, 24H),1.68 (s, 3H), 1.74 (s, 3H), 1.9-2.1 (m, 36H), 3.18 (d, 2H, J = 7.2 Hz), 3.99 (d, 6H, J = 4.2 Hz), 4.94 (t, 1H, J = 6.3 Hz), 5.10 (m, 9H); ^{13}C NMR δ 11.95 (CH_3), 16.03, (CH_3) 16.36 (CH_3), 17.69 (CH_3), 25.32 (CH_2), 25.71 (CH_3), 26.53 (CH_2), 26.72 (CH_2), 26.77 (CH_2), 39.55 (CH_2), 39.74 (CH_2), 39.76 (CH_2), 61.14 (CH_3), 118.85 (CH), 123.85 (CH), 124.15 (CH), 124.26 (CH), 124.41 (CH), 131.23 (CH), 134.93 (CH), 135.00 (CH), 135.25 (CH), 137.63 (CH), 138.86 (CH), 141.68 (CH), 144.21 (CH), 144.36 (CH), 183.91 (C), 184.76 (C).

2,3-Dimethoxy-5-methyl-1,4-benzoquinone (39).[52] ^{1}H NMR δ 2.04 (d, 3H, J = 1.8 Hz), 4.00 (s, 3H), 4.03 (s, 3H), 6.44 (d, J = 1.5 Hz); ^{13}C NMR 15.46, 61.18, 61.24, 131.27, 144.03, 144.81, 145.00, 184.16, 184.39.

2-Methoxy-1,4-benzoquinone (40).[78] 2-Methoxy-1,4-hydroquinone (1.4 g, 10 mmol) was oxidized with CAN (21.92 g, 40 mol) in 75% acetonitrile / water (80 mL) to give **40** (0.59 g, 60%). Recrystallization from EtOH / water gave 0.53 g, mp . ^{1}H NMR δ 3.84 (s, 3H), 5.96 (s, 1H), 6.72 (s, 2H); ^{13}C NMR δ 56.25, 107.72, 134.47, 137.26, 158.63, 181.72, 187.46.

2,3-Dimethoxy-1,4-benzoquinone (41).[79] To a solution of 2,3-dimethoxyphenol (0.308 g, 2 mmol) in MeOH (5 mL) was added 60 mL of water and 2 mL of 2N NaOAc. Fremy's salt ($\cdot$O-N(SO_3K)$_2$, 1.206 g, 4.5 mmol) was added and the solution became violet. After cooling to 0 °C in an ice bath (5 min) the mixture was extracted with $CHCl_3$ (3 x 40 mL). The chloroform layers were combined, washed (NaCl), dried ($MgSO_4$), filtered and concd (rotary evaporator) to yield 0.271 g, 81%. Recrystallization from hexane gave 0.180 g, mp 62-63 °C (lit[50] 66-67 °C); ^{1}H NMR δ 4.03 (s, 6 H), 6.61 (s, 2H); ^{13}C NMR

61.30, 134.67, 145.15, 184.10; HRMS calc for $C_8H_8O_4$ 168.0422, found 168.0424.

2,6-Dimethoxy-1,4-benzoquinone (42).[52] ^{1}H NMR δ 3.83 (s, 6H), 5.86 (s, 2H); ^{13}C NMR δ 56.50, 107,42, 157.30, 186.85, 189.48.

2-Methoxy-5-methyl-1,4-benzoquinone (43). ^{1}H NMR δ 2.07 (d, 3H, J = 1.5 Hz), 3.83 (s, 3H), 5.94 (s, 1H), 6.56 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ 15.78, 56.25, 107.58, 131.26, 146.86, 158.72, 182.12, 187.65.

2-Methoxy-6-methyl-1,4-benzoquinone (44).[79] The oxidation of 2-methoxy-6-methylphenol with Fremy's salt as described for **41** yielded **44** (0.598 g, 98%); mp 149-150 °C (Et_2O); ^{1}H NMR δ 2.06 (d, 3H, J = 1.8 Hz), 3.81 (s, 3 H), 5.88 (d, 1 H, J = 2.4 Hz), 6.54 (s, 1H); ^{13}C NMR δ 15.53, 56.28, 107.32, 133.85, 143.64, 158.80, 182.38, 187.43; HRMS calcd for $C_8H_8O_3$ 152.0473; found 152.0474.

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(74) The distillation was stopped at 125 °C ot, 1.0 mm Hg. The residual solid in the distillation flask was recrystallized (hexanes / $CHCl_3$) and determined to be 4,4'-dimethyl-2,2',5,5'-tetramethoxybiphenyl, mp 132-133 °C; ^1H NMR δ 2.27 (s, 3 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 6.77 (s, 1 H), 6.81 (s, 1 H); ^{13}C NMR δ 16.40, 55.97, 56.62, 113.84, 114.89, 125.53, 126.50, 150.67, 151.47; MS *m/z* 302.

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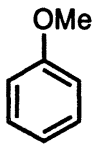
APPENDIX A

GLOSSARY OF STRUCTURES



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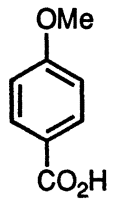

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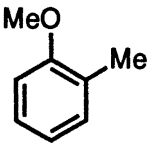

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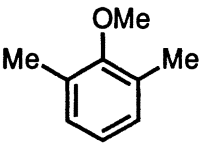

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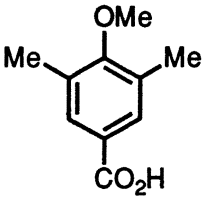

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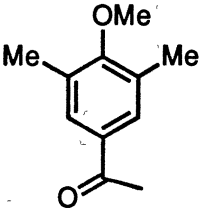

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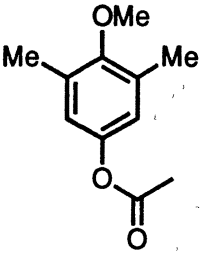

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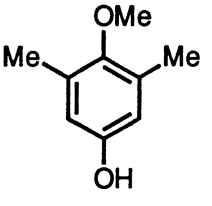

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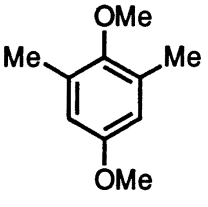

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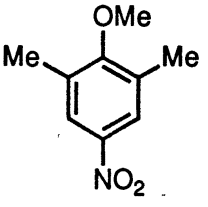

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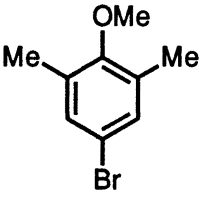

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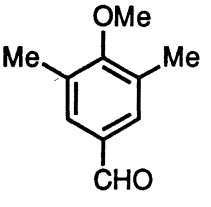

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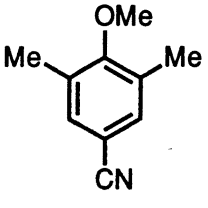

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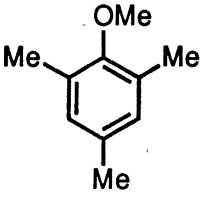

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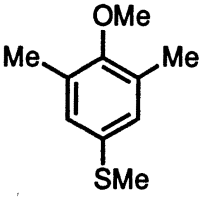

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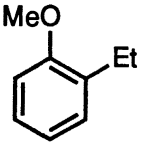

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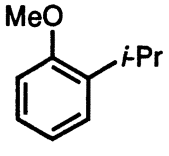

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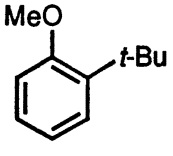

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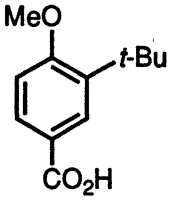

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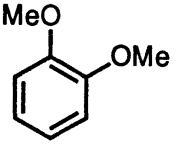

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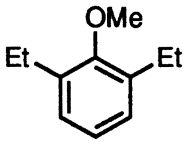

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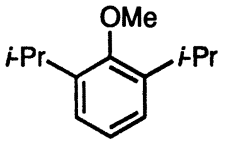

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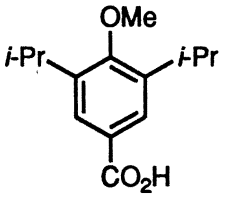

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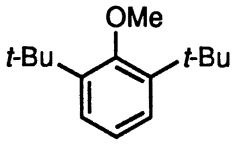

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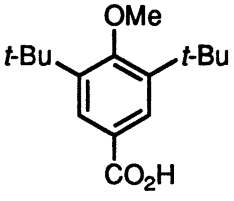

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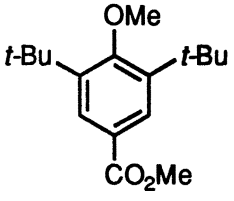

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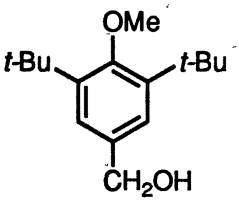

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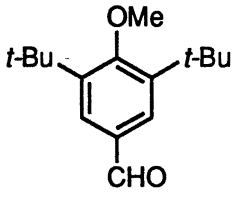

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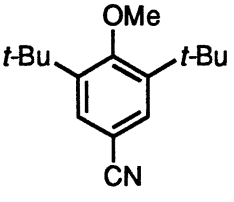

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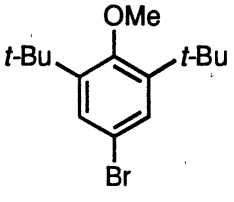

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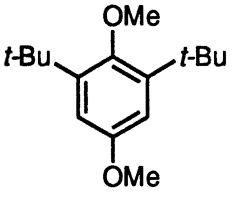

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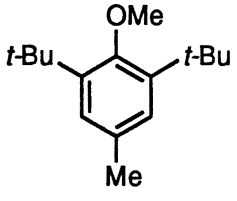

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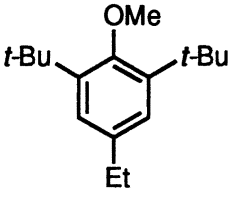

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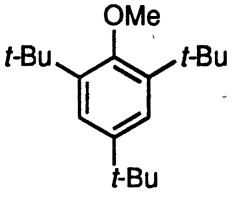

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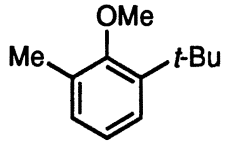

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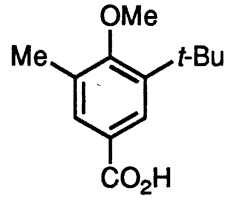

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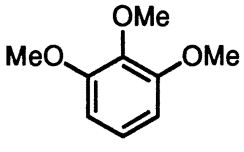

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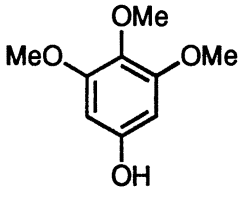

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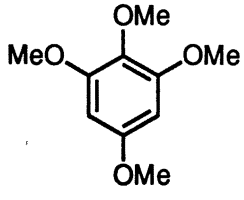

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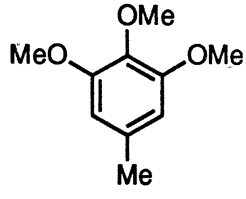

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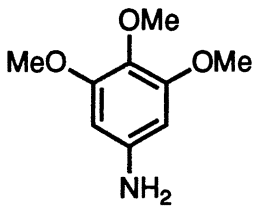

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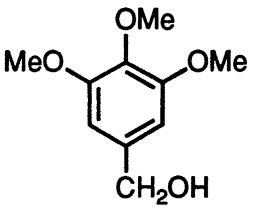

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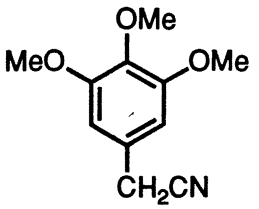

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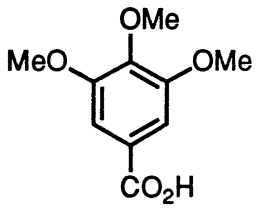

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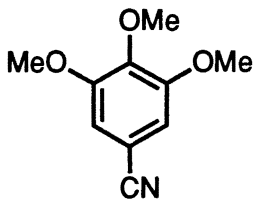

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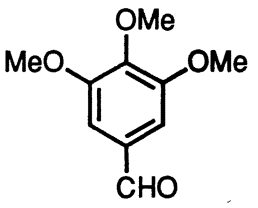

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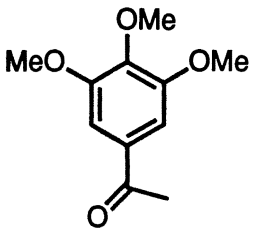

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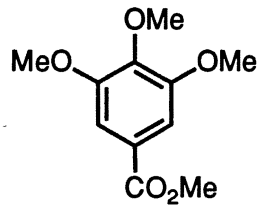

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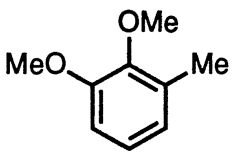

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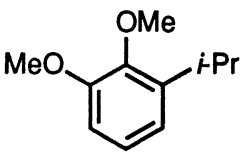

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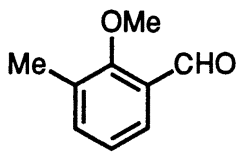

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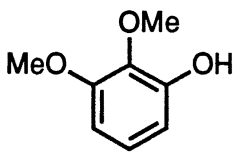

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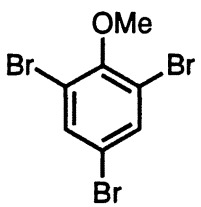

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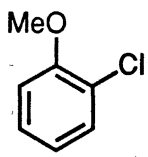

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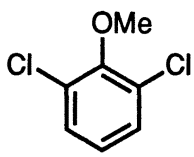

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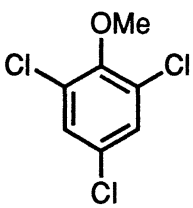

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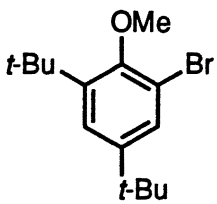

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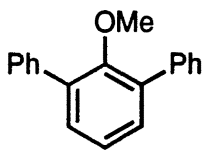

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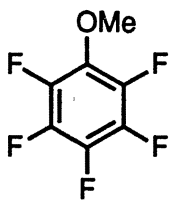

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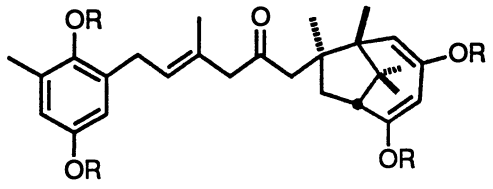

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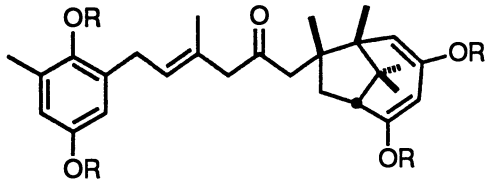

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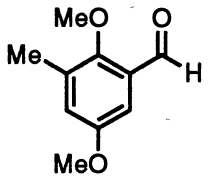

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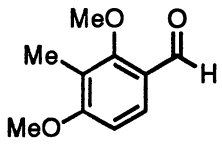

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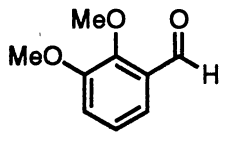

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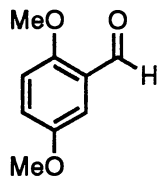

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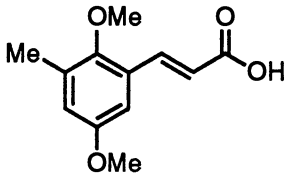

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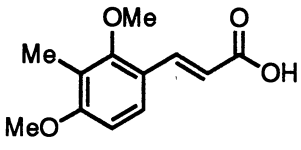

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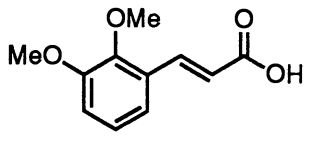

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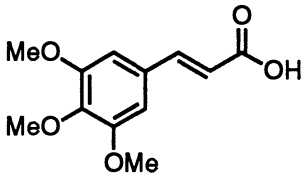

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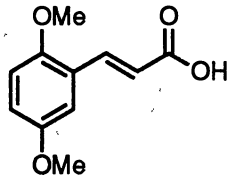

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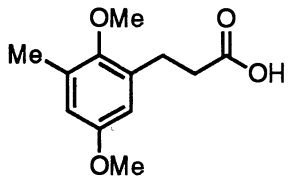

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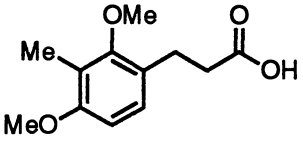

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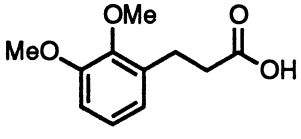

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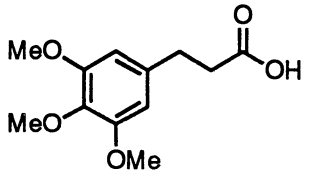

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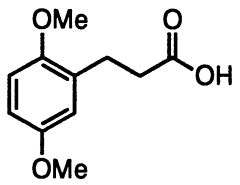

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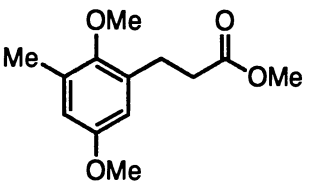

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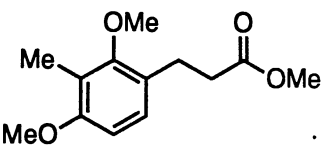

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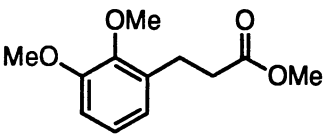

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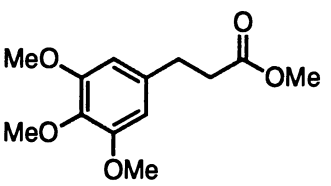

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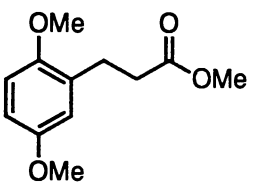

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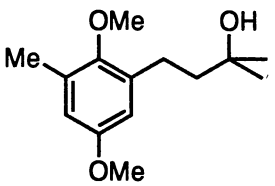

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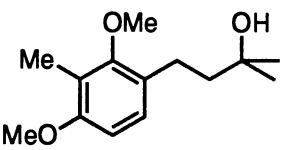

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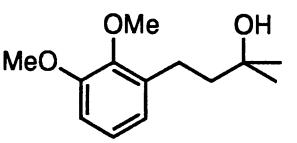

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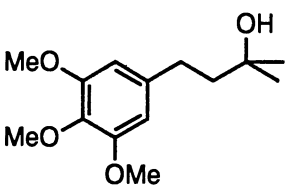

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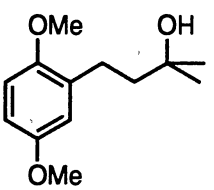

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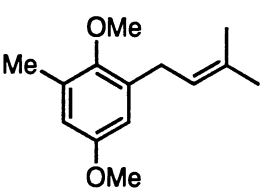

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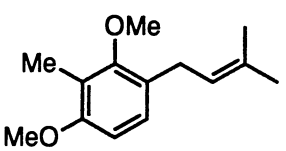

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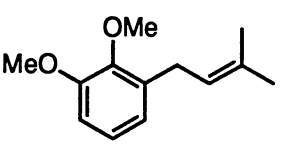

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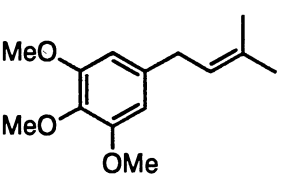

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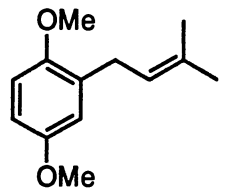

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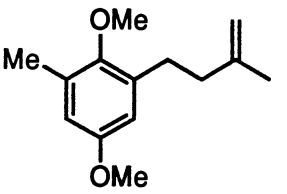

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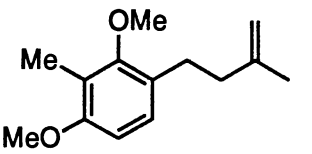

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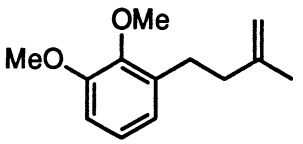

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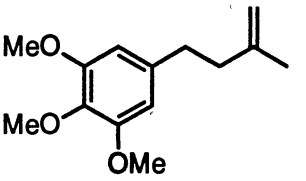

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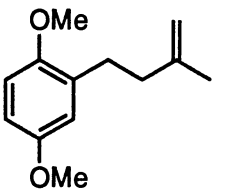

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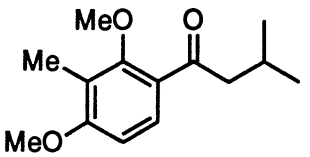

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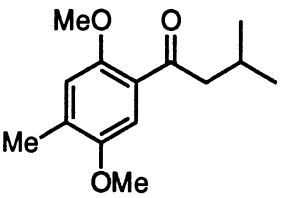

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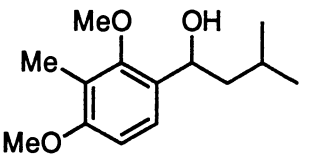

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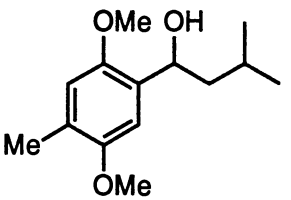

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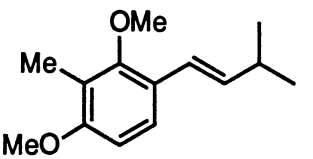

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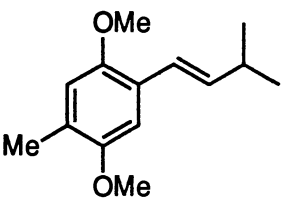

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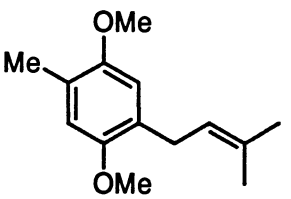

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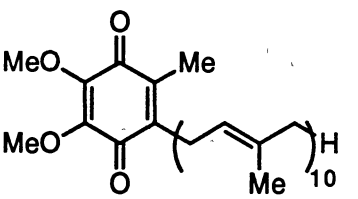

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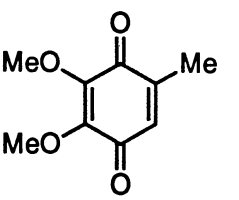

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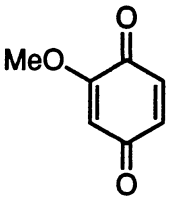

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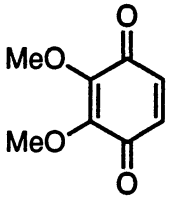

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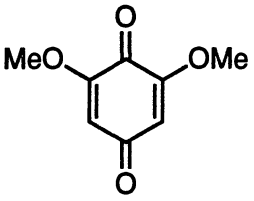

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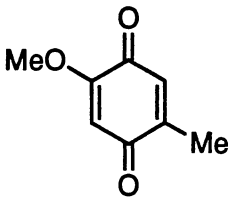
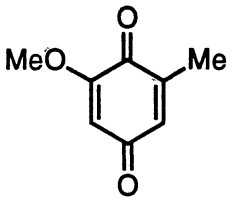


43



44

APPENDIX B

SELECTED NMR SPECTRA

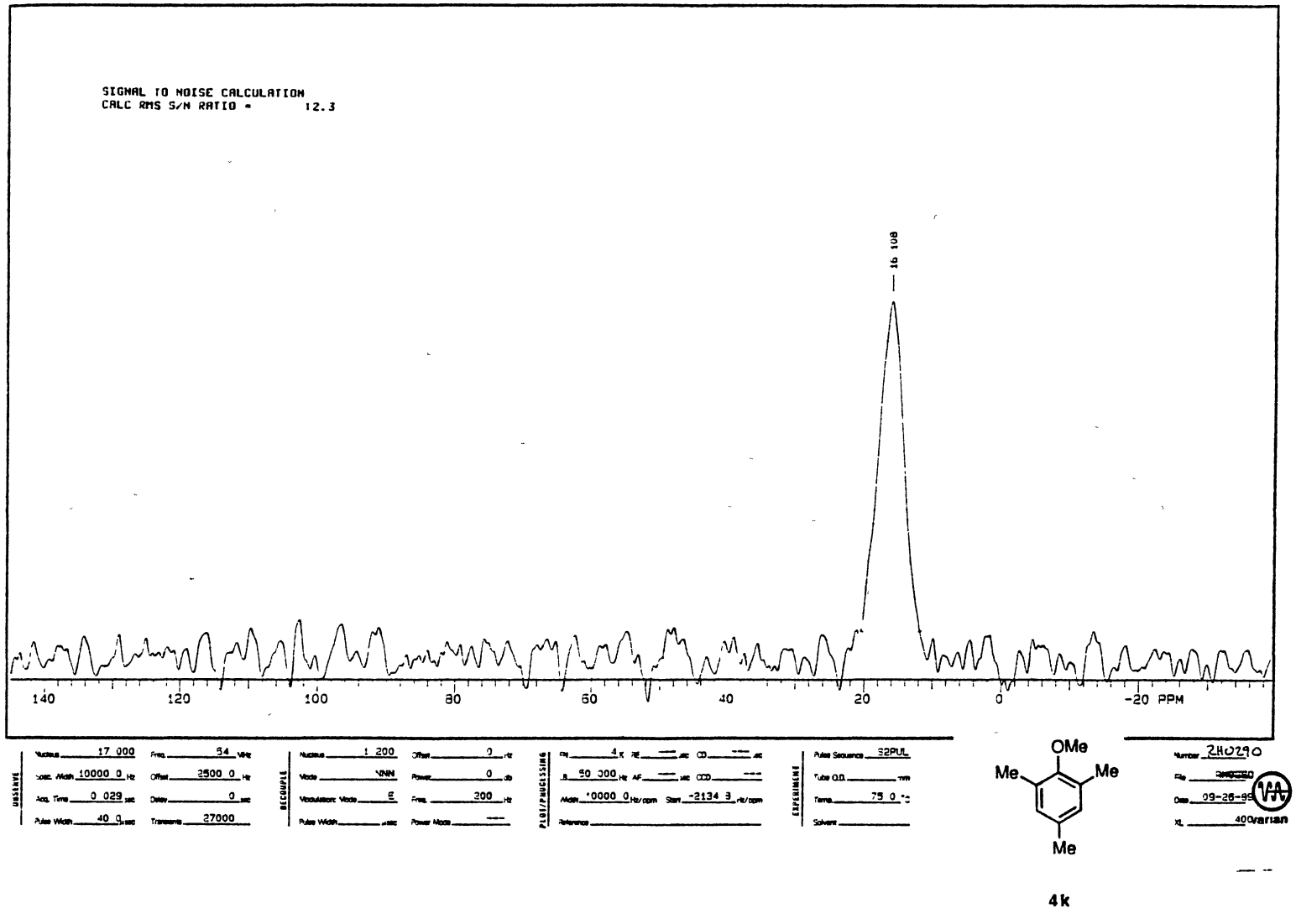
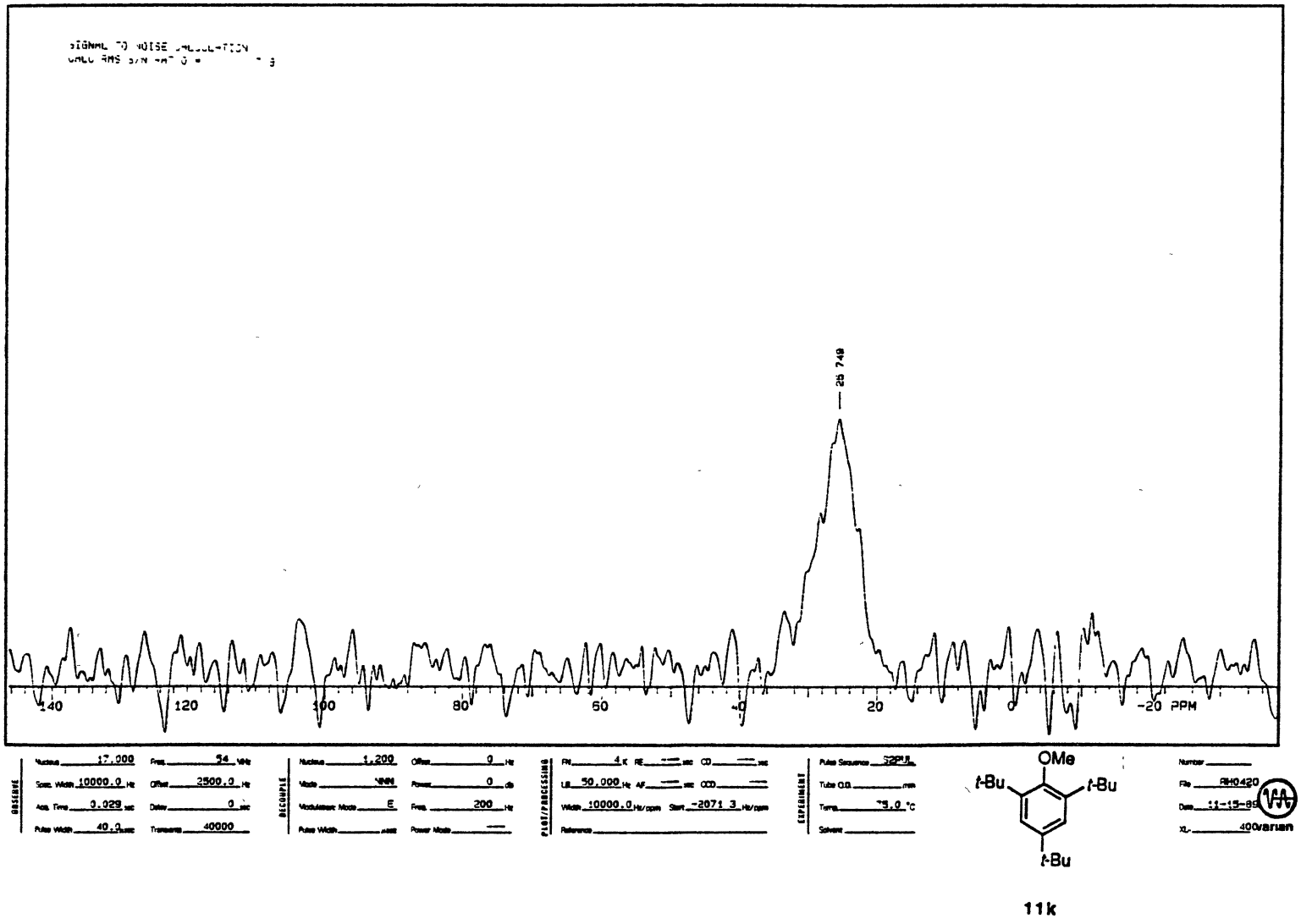
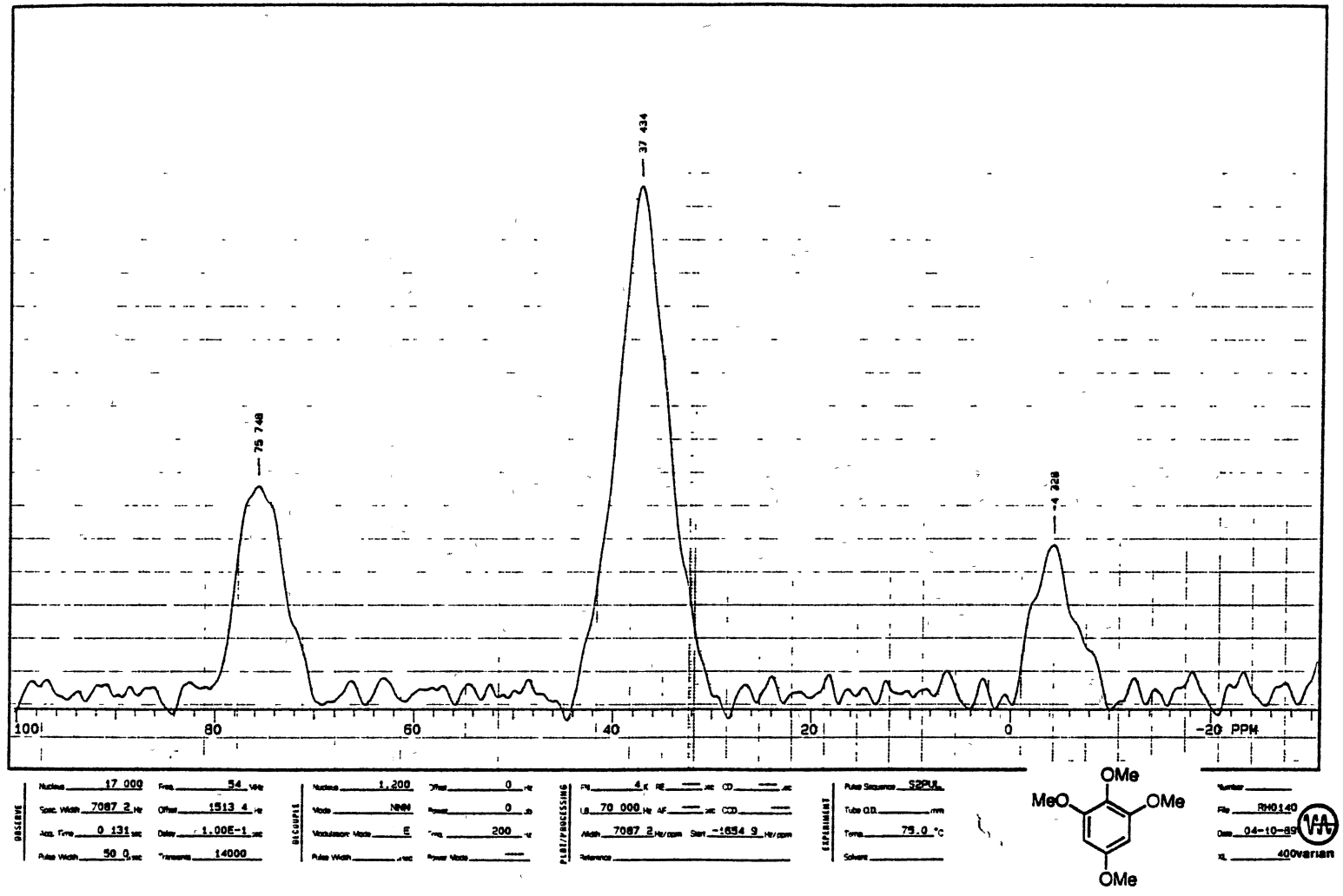


Figure 16. ^{17}O NMR spectrum of **4k**.



11k

Figure 17. ^{17}O NMR spectrum of **11k**.



13c

Figure 18. ^{17}O NMR spectrum of **13c**.

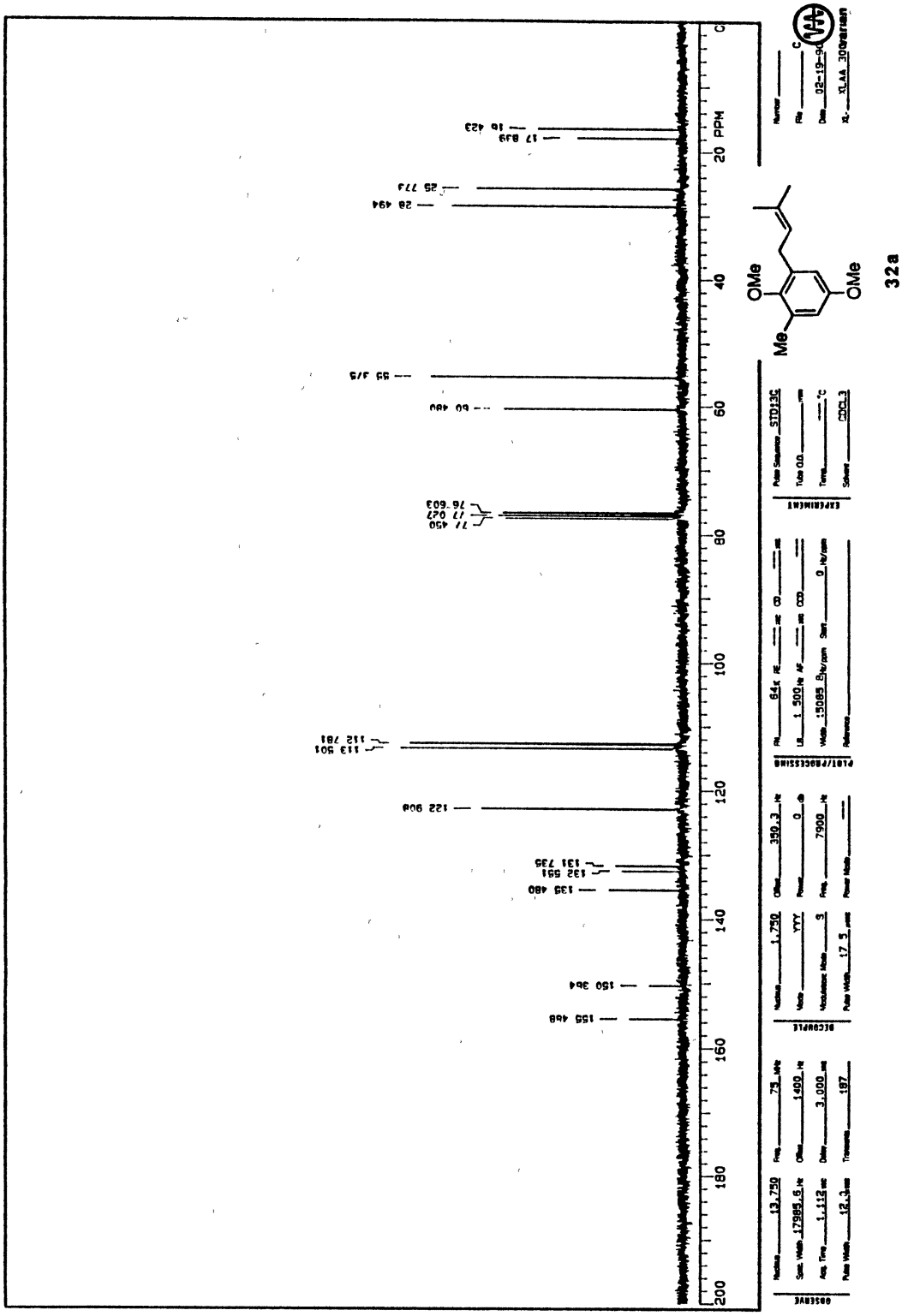


Figure 19. ^{13}C NMR spectrum of **32a.**

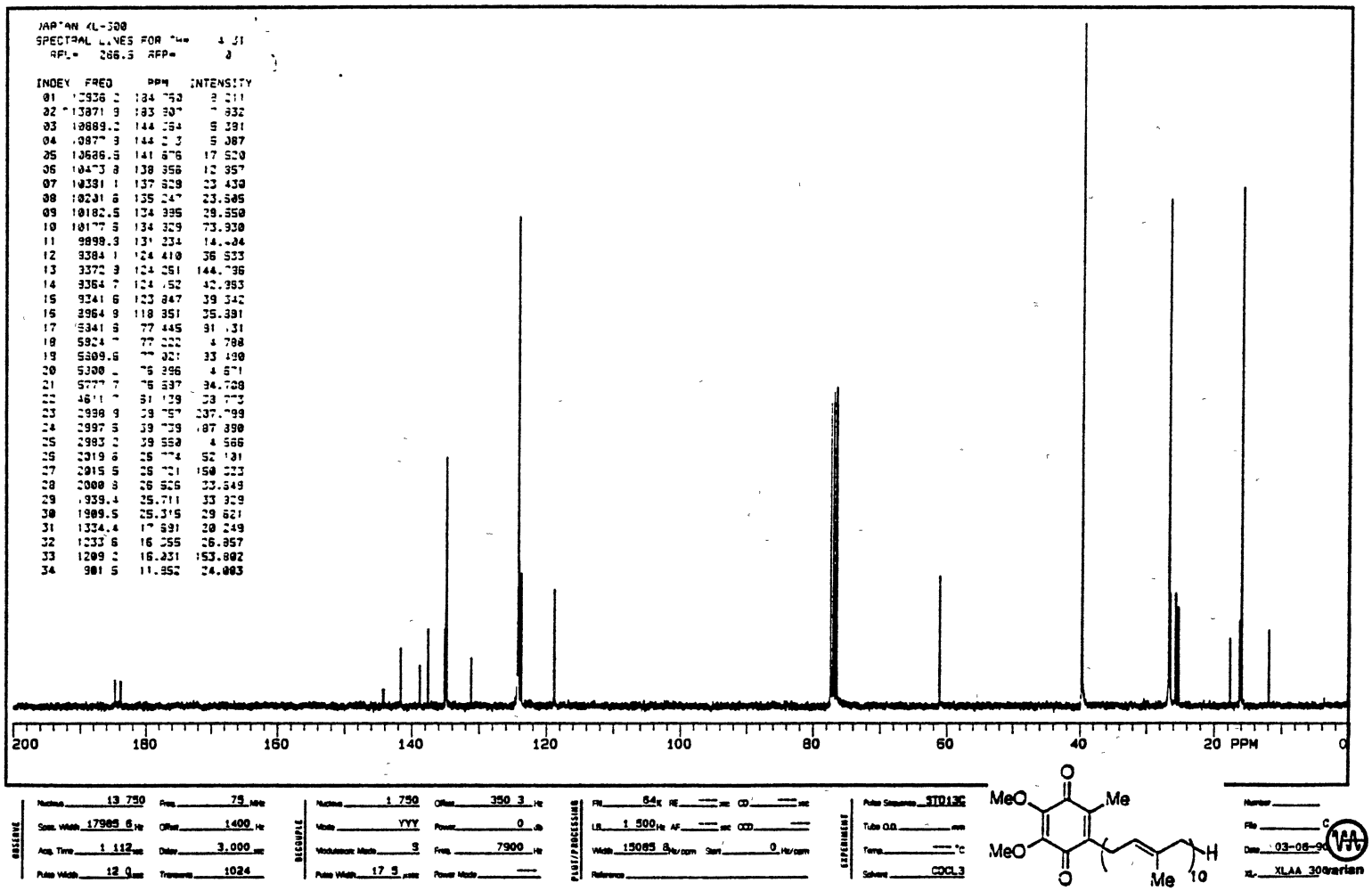


Figure 20. ^{13}C NMR spectrum of 38.

38

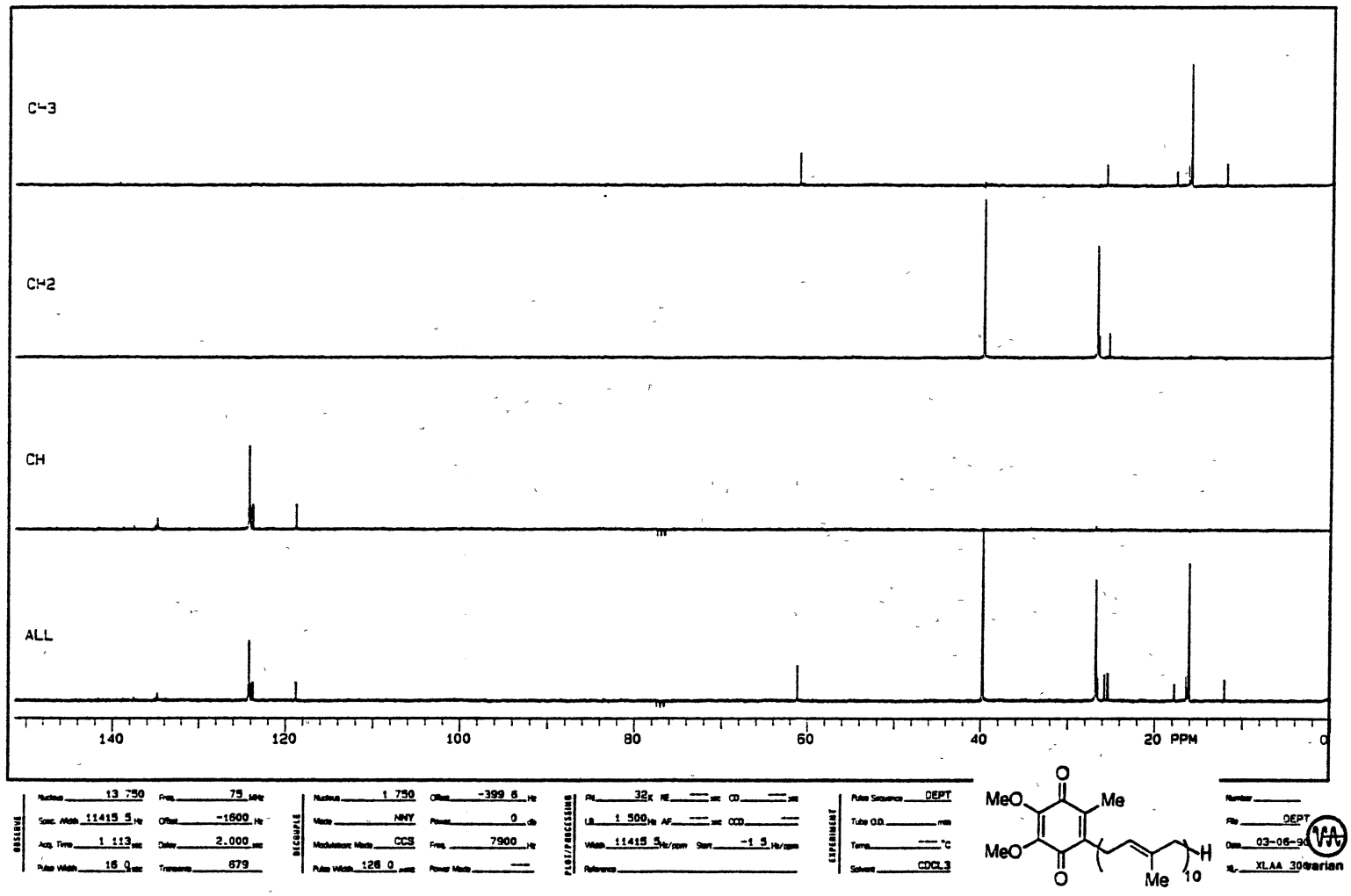
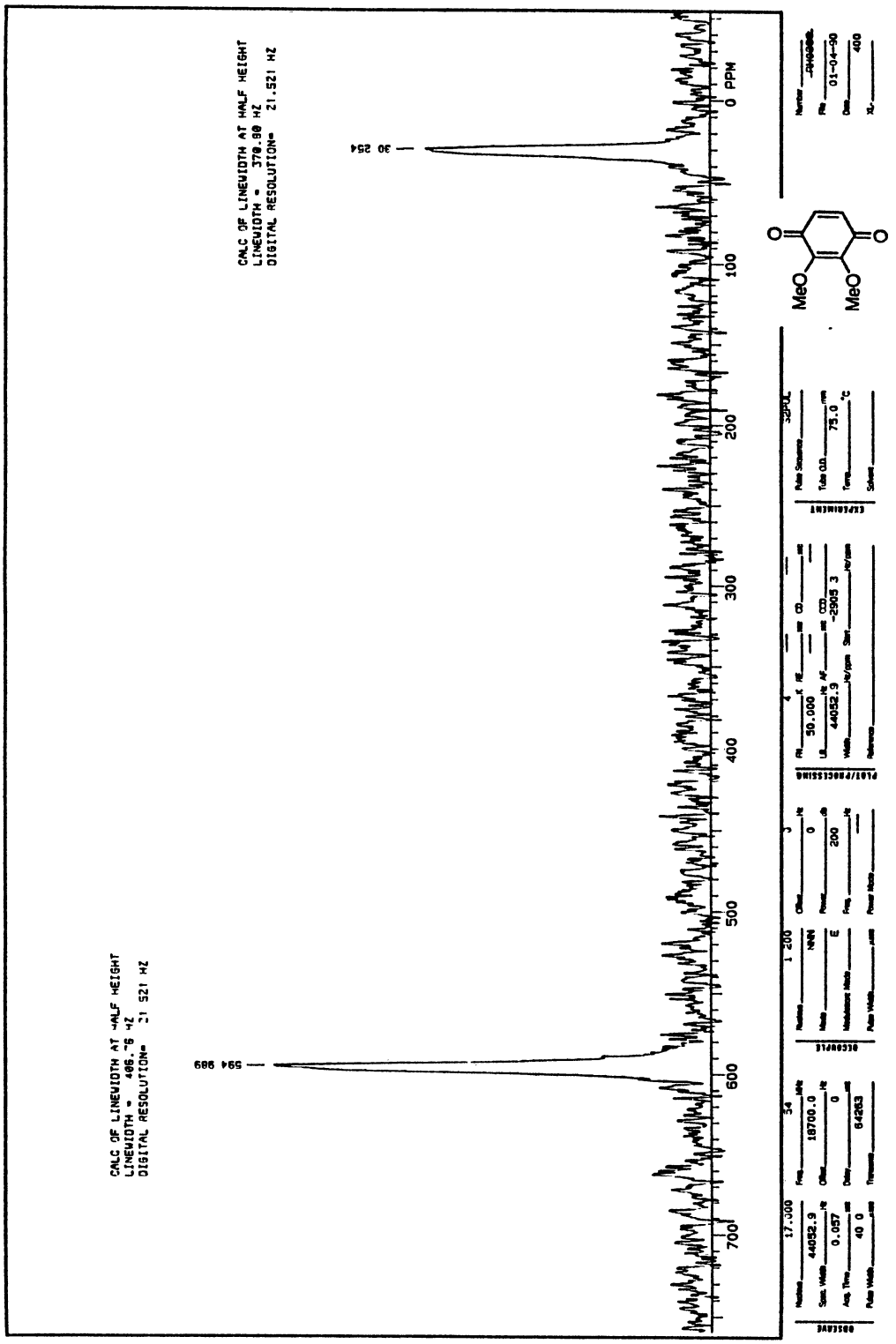


Figure 21. DEPT NMR spectrum of 38.

38



41

Figure 22. ^{17}O NMR spectrum of **41.**

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